



AWARENESS

Newer Horizons in Human Excellence



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Scope of the Journal

Mission Statement

The Journal exists to promote, protect, and propagate novel findings, deeper insights, and profound wisdoms within and across all fields of human knowledge, behavior, and endeavor. Fueled by a love for humanity, a child-like curiosity, and a laser-like focus on truth, this Journal provides a space for creative ideas “Where tireless striving stretches its arms towards perfection; Where the mind is led forward by thee into ever-widening thought and action...” (Rabindranath Tagore, 1861-1941).

Scope of the Journal

Awareness is a multidisciplinary, open access, research journal of The Sathya Sai University for Human Excellence supported by an international editorial board that serves as an outlet for multidisciplinary and cutting-edge research within and across all the fields of human knowledge, behavior, and endeavor. *Awareness* provides space for investigations in all scientific disciplines, all fields of the arts and humanities, as well as all areas of business and commerce. This journal seeks to erase the blurring boundaries between various disciplines or fields of study and, therefore, it encourages the publication of collaborative, transdisciplinary research projects.

Awareness serves as a discussion forum for important issues related to advances in human excellence by publishing material on diverse points of view. The articles published in *Awareness* (including all articles, editorials, news, and commentaries, or book reviews) are signed by their author(s) and reflect the individual views of the author(s) and not the official perspectives of the University or the institutions with which the authors are affiliated.

Awareness seeks to publish those papers that are most influential in their fields or across different fields and that will significantly advance human knowledge, societal advancement, or human excellence in all aspects. Articles will be selected if they present innovative methods, important data, hypotheses, data syntheses, or related concepts. All contributions should merit recognition by the wider academic community, policy makers, and the general public provided by its publication in *Awareness*, beyond the recognition and societal impact that comes from publishing in more specialized journals.

Awareness welcomes submissions from all fields of human endeavor and from any source. The editors are committed to the prompt evaluation and publication of submitted papers while upholding high standards that support the validity and reproducibility of published research.

The types of articles accepted for publication include original research articles, brief reports, case studies, editorials, essays, hypotheses, perspectives, study protocols, narrative and systematic reviews, book reviews, and selective case reports (see next article for details). Consistent with the University policy of providing free education to all students, no publication charges will be levied to any authors or contributors. Web-based Open Access will be assured to all subscribers and non-subscribers completely free-of-cost. All published items will be assigned a digital object identifier (DOI) and will be citable, whereas posters, video or audio files, and slide presentations will be published online as Supplementary Materials and will be available in the *Awareness* repository.

The Lead Author of each article must select from the following Journal Sections, Fields of Research, Subjects, and Topic Areas listed below. This will allow for the identification of appropriate reviewers as well as their article's placement in the journal.

Journal Sections

1) Scientific Disciplines

- a) Life Sciences: Anthropology, Ecology, Entomology, Botany, Zoology, Microbiology, Anatomy, Physiology, Evolution, Genetics, Marine Biology, Molecular & Cell Biology, Paleontology, Plant Biology, and Biochemistry
- b) Allopathic Medicine: Basic Sciences (Biochemistry, Bioengineering, Biomedical Data Science, Chemical & Systems Biology, Comparative Medicine, Developmental Biology, Epidemiology & Population Health, Genetics, Microbiology & Immunology, Molecular & Cellular Physiology, Neurobiology & Neurosciences, Structural Biology, Health Policy); Clinical Sciences (Anesthesiology, Cardiothoracic Surgery, Dermatology, Emergency Medicine, Internal Medicine, Neurology, Neurosurgery, Obstetrics & Gynecology, Ophthalmology, Orthopedics, Otolaryngology, Pathology, Pediatrics, Psychiatry & Behavioral Sciences, Radiology, Radiation Oncology, Surgery, Urology)
- c) Traditional Medical Sciences: Ayurveda, Homeopathy, Naturopathy, Siddha Medicine, Chinese Medicine, Acupuncture, Reiki.
- d) Complementary Medical Sciences: Osteopathy, Biofeedback/Hypnotherapy, Mind/body medicine, Chiropractic, Massage, Reflexology, Magnetotherapy, Therapeutic Touch, Aromatherapy, Physiotherapy
- e) Veterinary Sciences: Dermatology, Pathology, Animal welfare, Veterinary Biology, Epidemiology, Internal Medicine, Surgery, Nutrition, Theriogenology, Laboratory Animal Medicine, Dentistry, Emergency & Critical care, Microbiology, Pharmacology, Radiology, Radiation Oncology
- f) Pure Science: Mathematics, Physics, Chemistry
- g) Applied Sciences: Engineering, Architecture, Food Sciences, Forensic Sciences, Materials Science, Industrial Sciences, Pharmaceutical Sciences, Sports Sciences/ Physical Education
- h) Computer Sciences, Technology, & Robotics
- i) Agricultural Sciences
- j) Earth & Environmental Sciences → Geography, Geology, Ecology, Oceanography, Meteorology
- k) Social Sciences: Sociology, Psychology, Anthropology, Communication, Journalism, Criminology
- l) Yogic Sciences: Spirituality, Vedic Studies, Astrology
- m) Astronomy, Astrophysics, & Galactic Sciences

2) Arts and Humanities

- a) Performing Arts: Music, Theater, Comedy, Cinema, Acrobatics, Conducting, Directing, etc.
- b) Creative Arts: Fine Art, Sculpture, Tapestry, and others.
- c) Vocational Arts: Plumbing, Electrical, Welding, Assembly line, Printing, Graphics, Styling, Cosmetology, Esthetics, Child Life.
- d) Languages
- e) Economics: Macroeconomics, Microeconomics
- f) Philosophy
- g) History & Archeology
- h) Political Science
- i) Education
- j) Ethics & Morality
- k) Law & Judicial Studies
- l) Theology & Religious Studies

3) Business & Commerce

- a) Accounting
- b) Business Administration
- c) Business Analytics
- d) Business & Corporate Strategy
- e) Entrepreneurship
- f) Finance
- g) HR Management
- h) Management Science
- i) Management Information Systems
- j) International Trade & Business
- k) Logistics & Supply-Chain Management
- l) Sales & Marketing
- m) Market Research
- n) Operations Management
- o) Industrial/Organizational Psychology
- p) Organizational Behavior
- q) Public Relations
- r) Real Estate Management
- s) Insurance & Investing
- t) Actuarial Sciences

In this Issue...

The Inaugural Issue of this journal contains the few selected articles from the authors who responded to our call for submissions within the short timeframe available. The accompanying Editorial, *“Striving toward perfection”* connects this journal to the underlying roots of humanity’s quest for knowledge, explains the motivation for publishing peer-reviewed, open access articles resulting from cutting-edge, collaborative, team-driven, transdisciplinary research, and affirms our deep commitment to keeping the journal free from all monetary transactions or commercial interests. The Editorial further outlines three ways in which this journal differentiates itself from all other academic publications, and finally explains the journal’s name by connecting it to our spiritual roots.

The lead article in this issue is an essay on *“Theorizing a Humanizing Pedagogy of Love”* by Dr. Molina from the University of San Diego, USA. She issues a clarion call to return to the lost pedagogy of love, compassion, and empathy in all schools, colleges, and other learning environments. Based on scientific evidence, art, and contemporary thought, she provides a cogent rationale for using love and empathy as tools for centering our students, enhancing their emotional intelligence, leveraging their cultural, linguistic, and spiritual backgrounds, and building their sense of belonging, empowerment, and well-being. This conscious education approach, she posits, will significantly enrich student learning and ensure their flourishing in school and in society.

This humanities essay precedes a brief report on the *“Leading Causes of Life in Medicine: Pilot studies”*, where Dr. Cutts and Rev. Dr. Gunderson challenge the traditional, pathology-based models of care in modern medicine that are built on “the leading causes of death” and introduce instead a “leading causes of life” framework. The five Leading Causes of

Life include: connection, coherence, agency, intergenerativity, and hope; these were applied in the hospital setting for employee orientation, a primary care integrative medicine setting, a clergy conference for Chaplains, and for the annual physical exam of leaders from healthcare and other organizations. Their pilot data from surveys and feedback showed a significant positive impact in all four studies, giving impetus to growing calls for a significant shift in perspective for the practice of medicine.

In the next article titled “*Approaches to Unravel Complex Human Genetic Diseases*”, Drs. Ramachandra, Srushti, & Meghana provide a narrative overview of the evolving scientific methods used to understand the underlying causes, prevention, treatment, and management of genetic conditions over the past century. They systematically discuss tools such as pedigree and linkage analyses, cytogenetics, next-generation sequencing, personalized genomic medicine, and the artificial intelligence applications that geneticists apply to congenital and complex human genetic disorders.

An original article follows the broad overview of genetics titled, “*Vaginal Sacrocolpopexy in Vault Prolapse: A case series*” by Drs. Padmasri, Holla, & Keerthi examining the surgical approach, efficacy, postoperative complications, and longer term outcomes in a prospective study of rural women undergoing surgery for vault prolapse. They point out the clinical considerations involved in planning these surgical procedures and identify the factors associated with favorable and unfavorable outcomes. The novel findings from this case series result from systematic assessments of the long-term outcomes at 3 and 6 months after hospital discharge.

The last article is a narrative review on “*Definitions of Resilience in Childhood and Adolescence*”, where Lee, Rovnaghi, Carter, and Dr. Anand present multi-disciplinary perspectives on the definitions of resilience in infancy, childhood, and adolescence. They describe how resilience is viewed and measured in psychology and psychiatry, social sciences and legal contexts, clinical pediatrics, neurobiology, and cultural psychology. They trace the roots and underlying mechanisms of resilience to the child’s experiences in early life, finally presenting practical solutions to promote resilience across the lifespan through parenting, relationships, and spirituality.

In conclusion, the Inaugural Issue of this unique multidisciplinary journal provides a window into the wide variety of research that will be published in future issues, with each report seeking to explore “*newer horizons in human excellence*” and supporting the overall mission of the world’s first-ever University for Human Excellence.

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*Inaugural Issue***Awareness: Types of Articles**

During the process of manuscript submission, the Lead Author of each article must select one article type from those listed below, and then follow specifications of that article type. All articles must also identify their subject area, depending on the content and direction of their research (see Scope of the Journal). Both these are useful to readers, informing them of the style and content of that article, as well as for indexing services and databases, for applying filters to their search engines. Editors have the final say on which article type will be assigned to a published article. While the length of article may vary, contributors are encouraged to publish their experimental, theoretical, descriptive studies and observations in as much detail as possible – so that others in the same field can reproduce the published results. Incomplete and unspecified manuscripts will not be accepted for editorial review.

1. Original Article

These are original research manuscripts. The work should report original research and present a substantial amount of evidence-based novel information. The article should include the most recent and relevant references in the field. Each original should include a structured Abstract (250 words), Main findings (100 words), 5-7 Keywords, Introduction, Materials and Methods, Results, Discussion, and Conclusions sections, with a maximum word count of 3000 words, total 5 figures and/or tables, and a maximum of 75 references.

2. Brief Report

Brief reports are short, observational studies that report preliminary results, with a completed study or protocol. Brief reports can contain two figures and/or tables; however, the Materials and Methods sections should be detailed to ensure reproducibility of the presented work. The structure is similar to that of an article, and with a maximum word count of 1500 words and 20 references.

3. Clinical Trial

These communications are articles that present groundbreaking preliminary results or significant findings that are part of a larger study over multiple years. They can also include cutting-edge methods or experiments, and the development of new technology or materials. The structure is similar to an original article with maximum word count of 4000 words and 75 references.

4. Editorial

These are peer-reviewed commentaries used to announce the launch of new section, or a Special Issue, or an invited editorial. The main text should provide a brief introduction of the purpose and aim of the Editorial. Editorials should not include unpublished or original data, although if included, they must provide a Conflict of Interest statement from potential co-authors. Editorials do not require any Abstract and have a maximum word count of 1500 words and 20 references.

5. Essay

Essays are an article type commonly used in humanities and social sciences to present provocative arguments aimed to stimulate the readers' re-thinking of certain issues. The structure is similar to that of a review, with a suggested maximum word count of 6000 words, supported by up to 150 relevant references.

6. Hypothesis

These articles introduce a new hypothesis or theory, or a novel interpretation of a previously known theory. They should provide: (1) a novel interpretation of recent data or findings in a specific area of investigation; (2) an accurate presentation of previously posed hypotheses or theories; (3) the hypothesis presented which should be testable in the framework of current knowledge; and (4) consider the possible inclusion of original data as well as personal insights and opinions. If new data are presented, the structure should follow that of an article. If no new data are included, the structure is more

flexible, but should still include an Abstract, Keywords, Introduction, Relevant sections, and Concluding Remarks, with a suggested maximum word count of 4000 words and up to 50 references.

7. Opinion/Viewpoint

Opinions are short articles that reflect the author's viewpoints on a particular subject, technique, or recent discoveries. They should highlight the strengths and weaknesses of the topic presented in the opinion. The structure is similar to a review article; however, they are significantly shorter and focused on the author's perspective rather than a comprehensive review of the knowledge (or scientific evidence) in that area. The suggested maximum word count is 1000 words and 10 references.

8. Perspective

Perspectives are usually invited articles that showcase current developments in a specific field, highlight policy implications of recent research, or analyze recent events in their field. Emphasis is placed on future directions for the field and on the personal assessment of the author and/or co-authors. Comments should be situated in the context of existing literature from the previous 3 years. The structure is similar to a review, with a suggested maximum word count of 1500 words and up to 15 references.

9. Project Report

Project reports are short and/or rapid announcements of project results and implications. They should include a research strategy or approach, the activities, technologies, and details of the project undertaken, conclusions, and recommendations for future directions in the field. The structure is similar to an original article, but permits a higher degree of flexibility. The maximum word count is 2500 words and 25 references.

10. Protocol

Study protocols provide the detailed step-by-step description of a novel method or technique. Methods should be robust and reproducible and should reference previously published articles that use similar methodology. Any materials and equipment used must be explicitly listed. Conditions (temperature, pH, duration), quantities, concentrations, and all measurements must be clearly specified. Critical timepoints and steps, as well as warnings, should be emphasized in the text. The structure should include an Abstract, Keywords, Introduction, Experimental Design, Materials and Equipment, Detailed Procedure, and Expected Results, with a maximum word count of 2500 words and 30 references.

11. Technical Note

Technical notes are articles focused on a new technique, method, assay, or procedure. These should describe important modifications or unique applications for the described method. Technical notes can also be used for describing a new software tool or computational method. The structure should include an Abstract, Keywords, Introduction, Materials and Methods, Results, Discussion, and Conclusions, with a suggested maximum word count of 2500 words and 30 references.

12. Systematic Review

Systematic review articles present a detailed investigation of previous research on a given topic that use clearly defined search parameters and methods to identify, categorize, analyze, and report aggregated evidence on a specific topic. The structure is similar to a narrative review, with a suggested maximum word count of 5000 words, but they must also include a Methods section and follow the PRISMA checklist (<http://prisma-statement.org/PRISMAStatement/Checklist>), including a complete PRISMA flow diagram in the main text (templates can be downloaded from the PRISMA website). Authors are encouraged to register their detailed protocols before data extraction, in a public registry such as PROSPERO (<https://www.crd.york.ac.uk/prospero/>) and include a statement about following the PRISMA guidelines and registration information in the Methods section.

13. Narrative Review

Reviews offer a comprehensive analysis of the existing literature within a field of study, identifying current gaps or problems. They should be critical and constructive and provide recommendations for future research. No new, unpublished data should be presented. The structure includes an Abstract, Keywords, Introduction, Relevant Sections, Conclusions, and Future Directions, with a maximum word count of up to 6000 words and 200 references.

14. Book Review

Book reviews are short literary criticisms analyzing the content, style, and merit of a book published within the past 12 months. Full book details must be provided at the beginning of the article. The structure should only include an Introduction and Discussion of critical points with no sections or conclusions, with a suggested maximum word count of 750 words and 5 references.

15. Case Studies

Business case studies describe real-life business scenarios where steps were taken to solve a problem effectively. Each case study must present a compelling argument that allows business management students and teachers, business managers, or entrepreneurs to learn from this real-world experience. The structure of this article includes an Executive Summary, Problem Statement, Solution Options, Cost-Benefit Analysis, Risk Assessment, Implementation, Results (profits, growth, market share, consumer surveys or feedback, etc.), Main Learnings, and Alternative Strategies; with a suggested maximum word count of 3000 words and 30 references.

16. Case Reports

A case report is a detailed report of the symptoms, signs, diagnosis, treatment, and follow-up of 1-4 patients. Each case report is a rapid short communication between busy clinicians who may not have time or the resources to conduct detailed research, but they can provide research ideas for basic and clinical scientists. Case Reports are only accepted for publication if they provide:

- a. generalizable new knowledge that can be applied to improve the clinical care of other patients with the same condition, OR
- b. illustrate or explain a novel physiological principle that was not well understood before, which leads to the design of additional new experiments, OR
- c. present a completely new genetic syndrome or novel genetic/epigenetic mechanism that was not described previously, OR
- d. describe the completely novel clinical presentation of a known/new disease (e.g. MIS-C in children with COVID-19 reported from UK in April 2020), OR
- e. describe the previously unreported complications of a commonly used drug (or combination of drugs) or commonly performed surgical or interventional procedures.

All authors must use the Word template available from the journal website for formatting before submitting their manuscripts (www.awarenessjournals.org). Submitted manuscripts are not accepted for editorial review if they are not formatted correctly. All published items will be assigned a digital object identifier (DOI) and be citable, and posters, videos, or PPT presentations can be published together as the Supplementary Materials. The following disclaimer will be published at the end of each article:

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*Inaugural Issue***Awareness: Instructions for Authors****Submission Checklist for Authors**

Please:

1. Read the Journal Overview to assess if your manuscript is suitable for this journal.
2. Use the Microsoft Word template to prepare your manuscript.
3. Make sure that issues about publication ethics, research ethics, copyright, authorship, figure formats, data and references format have been appropriately considered.
4. Ensure that all authors have approved the content of the submitted manuscript.
5. Simultaneous submission is **NOT ACCEPTABLE**. Manuscripts submitted to *Awareness* should not be published previously and should not be under consideration for publication in any other journal. This does not apply to an abstract published in a Conference Proceedings or Souvenir.

Manuscript Submission Overview**Submission Process**

Manuscripts should be submitted via the Editorial Manager™ platform customized for *Awareness*, which can be accessed through any web browser or via the journal's website (www.awarenessjournals.org). The submitting author, who is generally the Corresponding Author, is responsible for the manuscript during the submission and peer-review process. The submitting author must ensure that all eligible co-authors have been included in the author list (read the [criteria to qualify for authorship](#)) and that all authors have read and approved the submitted version of the manuscript. To submit your manuscript, register and log in to the submission website. All co-authors can see the manuscript details in the submission system, if they register and log in using the e-mail address provided during manuscript submission.

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BY: credit must be given to the creator.



ND: No derivatives or adaptations of the work are permitted.

Accepted File Formats

Authors are encouraged to use the Microsoft Word template to prepare their manuscript, which can be downloaded from the journal's website (www.awarenessjournals.org). Using the template file will substantially shorten the time for copy-editing and publication of accepted manuscripts. The total amount of data for all files must not exceed 120 MB. If this is a problem, please contact the Editorial Office at: Awareness.Horizon@gmail.com, for further instructions.

- Main Manuscript: Manuscripts prepared in Microsoft Word must be converted into a single file before submission. When preparing manuscripts in Microsoft Word, we encourage you to use the Awareness Microsoft Word template file. Please insert your graphics (schemes, figures, etc.) in the main text after the paragraph of its first citation.
- Supplementary files: May be any format, but it is recommended that you use common, non-proprietary formats where possible (see below for further details).
- All references must be in the "Numbered" style, ensuring that you use the consistent formatting all through. It is essential to include author(s) name (s), journal or book title, articles or chapter title (where required), year of publication, volume and issue (where appropriate), first and last page numbers. DOI numbers (Digital Object Identifier) are not mandatory but encouraged. Bibliography software packages like: EndNote, Zotero, Mendeley, and Reference Manager are recommended.

Disclaimer: Usage of the journal's article templates are exclusively intended for submission to the journal for editorial and peer-review, and strictly limited to this purpose, and cannot be used for posting online on preprint servers or any other websites (including the author's website).

Cover Letter

A cover letter must be included with each manuscript submission. It should contain the full author names and affiliations, and further details about identifying text removed from the manuscript. It should also be concise and explain why the content of the article is significant, placing the findings in the context of existing work, and why it fits the scope of the journal. Confirm that neither the manuscript nor any parts of its content are currently under consideration or published in any other journal. Any prior submissions of the manuscript to *Awareness* must be acknowledged.

If a manuscript is accepted for publication, we will add an icon linking to your [online ORCID profile](#) in the final version of the published paper.

Author Affiliation

All authors should list their current affiliation and the affiliation where most of the research was performed, which is being described in their manuscripts. We recommend adding as primary the affiliation where most of the research was conducted or supported, but please check with your institution for any contractual agreement requirements. It is very important that author names and affiliations are correct. Incorrect information can mean a lack of proper attribution or incorrect citation and can even lead to problems with promotion or funding. After the publication of an article, updates or corrections to the author's address or affiliation may not be permitted.

Independent Researcher

If any author is not currently affiliated with a university, institution, or company, or have not been affiliated during the development of the manuscript, they should list themselves as an "Independent Researcher".

Manuscript Preparation

General Considerations

Research manuscripts should comprise:

- Front matter: Title, Author list, Affiliations, Abstract (250 words), Keywords (5-7), Main Message (100 words).
- Research Manuscript sections: Introduction, Materials and Methods, Results, Discussion, Conclusions (see *Awareness*:

Types of Articles for other section headings).

- **Black matter:** Supplementary materials, Acknowledgments, Author Contributions, Conflicts of Interest, References, Disclaimer.

Review manuscripts should comprise the front matter, literature review sections, and the back matter. The Word template file can also be used to prepare the front and back matter of your review manuscript. Structured reviews and meta-analyses should use the same structure as research articles and ensure they conform to the [PRISMA guidelines](#).

• Graphical Abstract:

A graphical abstract (GA) is an image that appears alongside the text abstract in the Table of Contents. In addition to summarizing the content, it should represent the topic of the article in an attention-grabbing way. Moreover, it should not be exactly the same as the Figure in the paper or just a simple superposition of several subfigures. Note that the GA must be original and unpublished artwork. Any postage stamps, currency from any country, or trademarked items should not be included in it.

The GA should be a high-quality illustration or diagram in any of the following formats: PNG, JPEG, or TIFF. Written text in a GA should be clear and easy to read, using one of the following fonts: Times New Roman, Arial, Palatino, Helvetica, Calibri. The minimum required size for the GA is 560 × 1100 pixels (height x width). The size should be of high quality in order to reproduce well.

• **Acronyms/Abbreviations/Initialisms** should be defined the first time they appear in each of three sections: the abstract; the main text; the first figure or table. When defined for the first time, the acronym/abbreviation/initialism should be added in parentheses after the written-out form.

• **SI Units** ([International System of Units](#)) should be used. Imperial, US customary and other units should be converted to SI units whenever possible.

• **Equations:** If you are using Word, please use either the Microsoft Equation Editor or the MathType add-on. Equations should be editable by the editorial office and not appear in a picture format.

• **Research Data and supplementary materials:** Note that publication of your manuscript implies that you must will all materials, data, and protocols associated with the publication available to readers unless justified otherwise. Disclose at the submission stage any restrictions on the availability of materials or information. Read the information about Supplementary Materials and Data Deposit for additional guidelines.

• **Preregistration:** Where authors have preregistered studies or analysis plans, links to the preregistration must be provided in the manuscript.

Front Matter

These sections should appear in all manuscript types

• **Title:** The title of your manuscript should be concise, specific and relevant. It should identify if the study reports (human or animal) trial data, or is a systematic review, meta-analysis, or replication study. Please do not include abbreviated or short forms of the title, such as a running title or header. These will be removed by our Editorial Office.

• **Author List and Affiliations:** Authors' full first and last names must be provided. The initials of any middle names can be added. The PubMed/MEDLINE standard format is used for affiliations: complete address information including city, state/province, and country. At least one author should be designated as the Corresponding Author. The email addresses of all authors will be displayed on published papers and hidden by Captcha on the website as a standard. It is the responsibility of the corresponding author to ensure that consent for the display of email addresses is obtained from all authors. If an author (other than the corresponding author) does not wish to have their email addresses displayed in this way, the corresponding author must indicate as such at proofreading stages. After acceptance, updates to author names or affiliations will not be permitted.

- **Equal Contributions:** Authors who have contributed equally should be marked with a superscript symbol (*). The symbol must be included below the affiliations, and the following statement added: "These authors contributed equally to this work". The equal roles of authors should also be adequately disclosed in the author contributions statement. Please read the criteria to qualify for authorship.
- **Abstract:** The abstract should be a total of about 250 words maximum. The abstract should be a single paragraph and should follow the style of structured abstracts, but without headings: 1) Background: Place the question addressed in a broad context and highlight the purpose of the study; 2) Methods: Describe briefly the main methods or treatments applied. Include any relevant preregistration numbers, and species and strains of any animals used; 3) Results: Summarize the article's main findings; and 4) Conclusion: Indicate the main conclusions or interpretations. The abstract must be an objective representation of the article: it must not contain results which are not presented and substantiated in the main text and should not exaggerate the main conclusions.
- **Main Message:** Summarize the main "take-home" message from the article in a brief statement (up to 100 words).
- **Keywords:** Five to seven pertinent keywords need to be added after the abstract. We recommend that the keywords are specific to the article, yet reasonably common within the subject discipline.
- **Corresponding Author:** Add the contact details of the Corresponding Author here.

Research Manuscript Sections

- **Introduction:** The introduction should briefly place the study in a broad context and highlight why it is important. It should define the purpose of the work and its significance, including specific hypotheses being tested. The current state of the research field should be reviewed carefully and key publications cited. Please highlight controversial and diverging hypotheses when necessary. Finally, briefly mention the main aim of the work and highlight the main conclusions. Keep the introduction comprehensible to scientists working outside the topic of the paper.
- **Materials and Methods:** They should be described with sufficient detail to allow others to replicate and build on published results. New methods and protocols should be described in detail while well-established methods can be briefly described and appropriately cited. Give the name and version of any software used and make clear whether computer code used is available. Include any preregistration codes.
- **Results:** Provide a concise and precise description of the experimental results, their interpretation as well as the experimental conclusions that can be drawn.
- **Discussion:** Authors should discuss the results and how they can be interpreted in perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible, and limitations of the work highlighted. Future research directions may also be mentioned. This section may be combined with Results.
- **Conclusions:** This section is not mandatory but can be added to the manuscript if the discussion is unusually long.
- **Patents:** This section is not mandatory but may be added if there are patents resulting from the work reported in this manuscript.

Back Matter

- **Supplementary Materials:** Describe any supplementary material published online alongside the manuscript (figure, tables, video, spreadsheets, etc.). Please indicate the name and title of each element as follows Figure S1: title, Table S1: title, etc.
- **Author Contributions:** Each author is expected to have made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; or have

drafted the work or substantively revised it; AND has approved the submitted version (and version substantially edited by journal staff that involves the author's contribution to the study); AND agrees to be personally accountable for the author's own contributions and for ensuring that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature.

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Written informed consent for publication must be obtained from participating patients who can be identified (including by the patients themselves). Please state "Written informed consent has been obtained from the patients) to publish this paper" if applicable.

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In the text, reference numbers should be placed in square brackets [], and placed before the punctuation; for example [1], [1-3] or [1,3]. For embedded citations in the text with pagination, use both parentheses and brackets to indicate the reference number and page numbers; for example [5] (p. 10). or [6] (pp. 101-105).

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1. Author 1, A.B.; Author 2, C.D. Title of the article. Abbreviated Journal Name Year, Volume, page range.

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2. Author 1, A.; Author 2, B. Book Title, 3rd ed.; Publisher: Publisher Location, Country, Year; pp. 154-196.

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9. Title of Site. Available online: URL (accessed on Day Month Year). Unlike published works, websites may change over time or disappear, so we encourage you create an archive of the cited website using a service such as WebCite. Archived websites should be cited using the link provided as follows:

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Supplementary Materials, Data Deposit and Software Source Code

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Where ethical, legal or privacy issues are present, data should not be shared. The authors should make any limitations clear in the Data Availability Statement upon submission. Authors should ensure that data shared are in accordance with consent provided by participants on the use of confidential data.

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The data presented in this study are openly available in [repository name e.g., FigShare] at [doi, reference number [reference number]].

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Publicly available datasets were analyzed in this study. This data can be found here: [link/accession number]

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Restrictions apply to the availability of these data. Data was obtained from [third party] and are available [from the authors/at URL] with the permission of [third party].

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No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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For work where novel computer code was developed, authors should release the code either by depositing in a recognized, public repository or uploading as supplementary information to the publication. The name and version of all software used should be clearly indicated.

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Additional data and files can be uploaded as “Supplementary Files” during the manuscript submission process. The supplementary files will also be available to the referees as part of the peer-review process. Only Word or PDF file formats are acceptable.

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Research and Publication Ethics

Research Ethics

Research Involving Human Subjects

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If the study reports research involving vulnerable groups, an additional check may be performed. The submitted manuscript will be scrutinized by the editorial office and upon request, documentary evidence (blank consent forms and any related discussion documents from the ethics board) must be supplied. Additionally, when studies describe groups by race, ethnicity, gender, disability, disease, etc., explanations regarding why such categorization was scientifically necessary must be clearly stated in the article.

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The editors will require that the benefits potentially derived from any research causing harm to animals are significant in relation to any cost endured by animals, and that procedures followed are unlikely to cause offense to the majority of readers.

- Replacement of animals by alternatives wherever possible,
- Reduction in number of animals used, and
- Refinement of experimental conditions and procedures to minimize the harm to animals.

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If national legislation requires it, studies involving vertebrates or higher invertebrates must only be carried out after obtaining approval from the appropriate ethics committee. As a minimum, the project identification code, date of approval and name of the ethics committee or institutional review board should be stated in Section 'Institutional Review Board Statement'. Research procedures must be carried out in accordance with national and institutional regulations. Statements on animal welfare should confirm that the study complied with all relevant legislation. Clinical studies involving animals and interventions outside of routine care require ethics committee oversight as per the American Veterinary Medical Association. If the study involved client-owned animals, informed client consent must be obtained and certified in the manuscript report of the research. Owners must be fully informed if there are any risks associated with the procedures and that the research will be published. If available, a high standard of veterinary care must be provided. Authors are responsible for correctness of the statements provided in the manuscript.

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Registration

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- Final approval of the version to be published; AND
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Any change to the author list should be approved by all authors including any who have been removed from the list. The corresponding author should act as a point of contact between the editor and the other authors and should keep co-authors informed and involve them in major decisions about the publication. We reserve the right to request confirmation that all authors meet the authorship conditions.

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The academic or section editor, or an Editorial Board member in the case of a conflict of interest and of regular submissions will be notified of the submission and invited to perform an editorial pre-check. During the editorial pre-check phase, the academic editor will assess the suitability of the submission with respect to the scope of the journal, as well as the overall scientific soundness of the manuscript, including the relevance of the references and the correctness of the applied methodology. Section editors can decide to reject the manuscript, request revisions before peer-review, or continue with the peer-review process and recommend suitable reviewers.

Peer-Review

Once a manuscript passes the initial checks, it will be assigned to at least two independent experts for peer-review. A double-blind peer-review process is applied, where authors’ identities are not known to reviewers.

In the case of regular submissions, in-house assistant editors will invite experts, including recommendations by an Academic Editor. These experts may also include Editorial Board Members and Guest Editors of the journal. Potential reviewers suggested by the authors may also be considered. Reviewers should not have published with any of the co-authors during the past three years and should not currently work or collaborate with any of the institutions of the co-authors of the submitted manuscript. To guarantee impartial refereeing, the names of referees will be revealed only if the referees agree to do so, and after a paper has been accepted for publication.

Editorial Decision and Revision

All the articles, reviews and communications published in *Awareness* go through the peer-review process and receive at least two reviews. The in-house Editor will communicate the decision of the Academic Editor, which will be one of the following:

- **Accept after Minor Revisions:**

The paper is in principle accepted after revision based on the reviewer's comments. Authors are given 5-7 days for minor revisions.

- **Reconsider after Major Revisions:**

The acceptance of the manuscript would depend on the revisions. The author needs to provide a point-by-point response or provide a rebuttal if some of the reviewer's comments cannot be revised. A maximum of two rounds of major revision per manuscript are provided. Authors will be asked to resubmit the revised paper within a suitable time frame, and the revised version will be returned to the reviewer for further comments. If the required revision time is estimated to be longer than 2 months, we will recommend that authors withdraw their manuscript before resubmitting so as to avoid unnecessary time pressure and to ensure that all manuscripts are sufficiently revised.

- **Reject and Encourage Resubmission:**

If additional experiments are needed to support the conclusions, the manuscript will be rejected and the authors will be encouraged to re-submit the paper once further experiments have been conducted.

- **Reject and Decline Resubmission:**

The article has serious flaws, and/or makes no original significant contribution. No offer of resubmission to the journal is provided.

- All reviewer comments should be responded to in a point-by-point fashion. Where the authors disagree with a reviewer, they must provide a clear justification (with references, if needed).

Author Appeals

Authors may appeal a rejection by sending an e-mail to the Editorial Office of the journal. The appeal must provide a detailed justification, including point-by-point responses to the reviewers' and/or Editor's comments using an appeal form. Appeals can only be submitted following a "reject and decline resubmission" decision and should be submitted within one (1) month from the decision date. Failure to meet these criteria will result in the appeal not being considered further. The Managing Editor will forward the manuscript and related information (including the identities of the referees) to a designated Editorial Board Member.

The Academic Editor being consulted will be asked to provide an advisory recommendation on the manuscript and may recommend acceptance, further peer-review, or uphold the original rejection decision. This decision will then be validated by the Editor-in-Chief. A reject decision at this stage is final and cannot be reversed.

Promoting Equity, Diversity, and Inclusiveness within the Awareness Journal

The management and all Editors of *Awareness* are committed to appointing a diverse expert Editorial Board. Active promotion of Equity, Diversity, Inclusiveness, and Justice are also reflective in our multi-national and inclusive workplace. We are proud to create equal opportunities without regard to gender, ethnicity, sexual orientation, age, religion, socio-economic status, or national origin. There is no place for discrimination in our workplace all stakeholders of the *Awareness* journal are required to uphold these principles in high regard.

Prajñānam Brahma - Awareness is Divine

Sri Madhusudan Sai

Founder – Sri Sathya Sai University for Human Excellence

When the first man opened his eyes and looked around in wonder at the suspended stars in the night sky which twinkled and shimmered eternally, the golden disc at dawn which never missed its appointment with the earthlings, the soothing silver moon in the night that waxed and waned rhythmically, the mother earth with all her myriad inhabitants – animate and inanimate, minuscule and mighty, and the crest jewel of it all – the humankind with its endless enterprise and enquiry—he asked within himself – Where did all this come from? Who governs this? Where does it all go at the end?

The first man wondered wide-eyed in the wilderness seeking answers to these questions; and when he could not find the answers outside, he turned within in deep contemplation. That's how seekers and sages evolved out of ordinary beings, just like how a caterpillar transforms itself into a butterfly.

The answers were more of intuitive revelations than experimental conclusions—call it serendipity if you may! The first understanding that emerged from this process of deep enquiry was that—there is a definitive power, 'a creative force' that exists, and all creation has emerged from it. The second inference was that this power or force is not mechanical, but it is 'conscious and creative', for the kind of distinctive variety and the intelligent detailing of finer aspects in creation, is not possible by a dead unconscious power. Thirdly, this power has no beginning or end, for everything in creation is cyclic—be it days or nights, seasons, or situations, and even life and death. Just that some are shorter cycles, and some are longer. Upon keen observation, a student of science can easily draw striking parallels between the intuitive understanding of the sages of yore and the scientific conclusions of the modern scientists, that say that all matter is energy ($E=mc^2$) and that energy can neither be created nor be destroyed, but can only be transformed from one form to another. Thousands of years ago, much before all the modern scientific studies started announcing its empirical evidence about the universe and creation, *taittirīyopaniṣad* described the supreme creative force as – *satyam, jñānam, anantam*, which is to say that this power has three attributes – Existence, **Awareness** and Eternity. The *aitareyopaniṣad* defines divinity as awareness - *Prajnanam Brahma*, implying that all awareness is Divine and so also the ability to be aware of all things.

Simply put, it means that it exists, it is intelligent and that it can never be created or destroyed. This is exactly what scientists say now, well almost, except that they are still debating whether it is a conscious energy or an unconscious force of nature. However, with the newer frontiers of Quantum Mechanics and Unified Field Theory, the idea of a 'field' – a substratum to the entire universe, is gaining rapid acceptance. This field, consisting of four kinds of forces namely – gravitational, electromagnetic, weak nuclear force and strong nuclear force, seems to have an intelligent way of its own, leading to the creation of newer materials, its sustenance and destruction as well. Let's not forget that once upon a time people thought that the earth was flat, till they discovered that it was not! So, science is yet to discover what sages have already found.

In *sanātana dharma*, the term given to this power which exists and is conscious as well as eternal, is *brahman*. *brahman* is considered as the one without name and form, without attributes and qualities, without dualities and differences, though paradoxically, all the variety, beauty and apparent differences in creation are all due to that one, eternal, non-dual, unchanging *brahman*. How is that possible?

Let's take the example of electricity, which by itself is nothing but a force generated by the flow of electrons in a wire. But, when the same electric current passes through a bulb, it turns into light energy; when it enters a heater, it becomes heat energy; when it enters a fan, it becomes wind energy and so on. Though electric current by itself does not have any of the attributes of light, heat, or wind energy; yet its interaction with the various appliances transforms the essential electrical energy into all the other kinds of energies.

Similarly, the conscious and intelligent energy of *brahman* interacts with nature and generates everything, sustains them, and finally even destroys them. The subatomic particles interact to form atoms, which form molecules, elements, compounds, matter, plants, birds, animals, and humans, and when humans die, they disintegrate back into the same subatomic particles and energy. This cycle continues perpetually! Based on this cyclic nature of the work of *brahman*, three functions have been attributed to *brahman*, which are creation – *śṛṣṭi*, sustenance – *sthiti* and dissolution – *laya*.

Thus, this one changeless *brahman*, essentially energy, appears to manifest in all the changing things or masses of the universe. Just as all ornaments – be it bangles, rings, necklaces are nothing but modifications of gold, and though known by different names which are attributed to their different forms, they are essentially gold only; similarly, everything and everyone is essentially *brahman* only. This is the foremost preaching of *sanātana dharma*.

A rationalist may shake this *upanishadic* truth off as a mere philosophical statement stating that everything one experiences with the senses and the mind is absolutely real; but before that, let them go through the work of the three physicists who shared the Nobel Prize for 2022 in the field of Quantum Physics.

This Quantum Physics theory has been around for some time, may be over a century now, which says that the perceived reality is 'not real' and is influenced by the observer. Well, that in a way means that the world as we see is the way we see, only because we see it that way. So, without the seer, the seen won't be real! It almost makes anyone laugh at it, like just as the great scientist Albert Einstein did when he scoffed at his friend saying, 'do you really think that the moon is not there when you are not looking at it?' However convincing it may sound as an argument, the quantum theory refutes it and replies in a resounding yes!

Almost a century of arguments back and forth, and after several experiments that led to the conclusion that the whole universe is connected in some way and the observed is dependent on the perception of the observer, the entangled photon experiments led to this conclusion when John Clauser, Alain Aspect and Anton Zeilinger split the 2022 Nobel Prize in Physics "for experiments with entangled photons, establishing the violation of Bell inequalities and pioneering quantum information science." And with that the hope against all hopes of the quantum atheists in some 'hidden variables' that were yet to be discovered causing seemingly a telepathic connection between things in the universe crashed to the floor. And now we know that things are connected in some 'mysterious' way.

In an interesting episode from *bhṛguvalli* of *taittirīyopaniṣad*, the disciple-son *bhṛgu*, desirous of *brahmavidyā* approaches his father *vāruṇi*, to understand the truth of *brahman* that is behind all existence. *vāruṇi* being a perfect teacher, does not deploy the usual method of discoursing his disciple, but rather encourages *bhṛgu* to find answers to the question himself through self-inquiry, and only adds more clues to his query by asking him to investigate through questions like – 'where does all the creation come from?', 'what sustains it and where does it all go at the end?' He tells the son, "Know that; that is *brahman*." *bhṛgu* goes back to observe and contemplate on these questions and concludes that *anna* or food is *brahman* – '*annaṁ brahmeti vyajānāt*' – everyone is born out of food or *anna*; all are sustained by food and at the end all merge into food, which is to say, one creature becomes food for another in the food cycle. But father *vāruṇi* isn't satisfied and asks *bhṛgu* to further investigate. The dutiful disciple *bhṛgu*, does so obediently. After much contemplation, *bhṛgu* returns with a newer insight that *prāṇa* or life force is *brahman* – '*prāṇo brahmeti vyajānāt*' – all beings are born out of the life force, they live due to the life force and ultimately when the life force is withdrawn, they disappear as well. But yet again, *vāruṇi* is not satisfied and urges *bhṛgu* to think deeper. So, this time after due thinking, *bhṛgu* returns with a deeper insight that *manas* or mind is *brahman* – '*mano brahmeti vyajānāt*' – all is because of the mind or *manas*. It is the mind that directs the life force, according to which creation, sustenance and destruction of all beings eventuate. Therefore, the mind is the basis of all.

Unsurprisingly, the teacher-father *vāruṇi* is not impressed yet. So, *bhṛgu* goes back to meditate further only to return with a newer knowledge that intelligence or *vijñāna* is *brahman* – '*vijñānaṁ brahmeti vyajānāt*' – intelligence is the basis of everything, and all creation emerges into existence due to a certain intelligence that governs birth, growth, and death of all creatures. This instinctive intelligence is in-built in all, and this governs the mind and directs the *prāṇa*. *vāruṇi* is happy but still not satisfied with his son's answers and sends him back to further meditate upon all that he had been observing thus

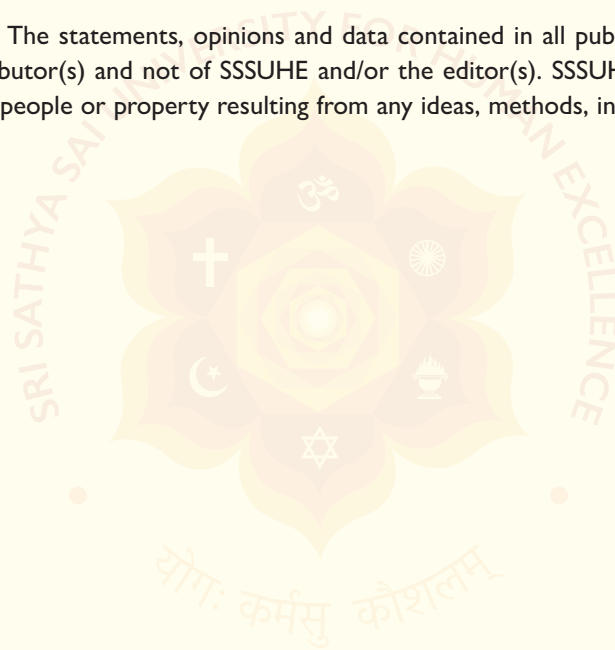
far. This time, after meditating deep and long, *bhṛgu* realises that *ānanda* or bliss is the basis of all existence – ‘*ānando brahmeti vyajānāt*’ – for the sake of seeking happiness all are born, all live, and finally perish.

bhṛgu loses himself in the experience of that *ānanda* and does not return to his father. So, this time *vāruṇi* scouts for his son and discovers that he has finally found the truth of brahman, which is that of the divine joy which is the basis of all creation.

Thus, ‘Constant Integrated Awareness’ about the truth within us – that space or presence which is eternal and peaceful is the ultimate thing to experience and realise, knowing which everything else is known.

This multidisciplinary journal of the Sri Sathya Sai University for Human Excellence brings not merely scientific but also spiritual enquiry into all investigations and inferences. The thin line between Science and Spirituality is getting increasingly thinner, and I am convinced that 21st Century Science shall finally meet with its other half of Spirituality, with greater awareness of their oneness.

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Editorial

Striving Toward Perfection

Kanwaljeet J. S. Anand, MBBS, D.Phil.¹; Shaun P. Setty, M.D.²

¹Professor of Pediatrics, Anesthesiology, Perioperative & Pain Medicine, Director, Stanford Child Wellness Lab, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA.

²Medical Director, Pediatric & Adult Congenital Cardiac Surgery, The Helen E. Hoag Endowed Chair in Pediatric Cardiovascular Surgery, Miller Children's Hospital & Long Beach Memorial Medical Center, Long Beach, California, USA.

Keywords: open access, multidisciplinary, free-of-cost, awareness

Corresponding Author: Dr. K. J. S. Anand Email: anandam@stanford.edu

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All human endeavour is formulated and fueled by the three fundamental attributes of being human – to desire, to act, and to know [1]. Desires motivate all humans – whether they pertain to the pursuit of material gains or goods, relationships or social connections, fame, fortune, recognition, and reputation, or even spiritual growth. Such motivations then activate our human agency [2], the power of humans “to act” using myriad skills and abilities to change our circumstances, environments, and/or experiences. The human agency to act seeks perfection; it lies behind most of the capabilities regarded as fundamental to human functioning by thinkers across the ages [3, 4] and in current times [5, 6]. It is also at the root of Karmic Law, the ancient law of cause and effect [7]. The natural consequence of all human action is knowledge, regardless of whether it results from reading a book, performing an experiment, eating food, or any other kind of action. We may have theoretical or imagined knowledge beforehand, but only after taking action, making an effort, do we gain experiential knowledge, regardless of whether this is new knowledge, or variations of prior knowledge, or altered perspectives based on experience. The coupling between action and knowledge is inextricable, and feeds our deep-seated desires to know, to know more, to know with greater clarity and certainty.

Citation: Anand KJS, Setty SP.
Awareness: Newer Horizons in Human Excellence, 1 (1): 27-29

Academic Editor: None

Received: 12-27-2023

Revised: 01-04-2024

Accepted: 01-04-2024



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This Journal was envisioned to promote and propagate the knowledge gained from novel research findings, to expound deeper insights and profound wisdoms by integrating knowledge across all fields of enquiry, by ambitiously pushing the frontiers of collaborative and empirical research. Fueled by love for humanity, child-like curiosity, and laser-like focus on the truth, this multidisciplinary, international Journal was inspired by the words of poet-philosopher Rabindranath Tagore (1861-1941) “Where tireless striving stretches its arms towards perfection; Where the mind is led forward by thee into ever-widening thought and action...” and, like Tagore, we aim to create a publicly shared space for such revitalizing, creative knowledge. Because the nature of light is to spread in all directions, so must this light of knowledge be shared freely and openly among all human beings to dispel the darkness of ignorance, inspiring each one to seek newer horizons in human excellence through their own efforts. Only then will the Journal fulfill the promise of its affiliation with the world's one-and-only University for Human Excellence.

Consequently, we are launching this as an open access, peer-reviewed, online journal that will publish investigations in the currently known and not-yet-known disciplines of science and technology, all fields of the arts and humanities, as well as all aspects of business, trade, and commerce. Unfettered from the traditions of academia, we seek to erase the blurring boundaries between various disciplines and fields of study. We, therefore, encourage the publication of collaborative, team-driven, multidisciplinary research projects in the form of original research articles, brief reports, case studies, editorials, essays, hypotheses, perspectives, study protocols, narrative and systematic review articles, book reviews, and selective case reports. Consistent with the University's policy and practice of providing completely free education to all students, no publication charges will be levied on any authors or contributors, and web-based Open Access will be assured to all subscribers and non-subscribers free-of-cost. The manuscript submission and review process workflow, as well as editorial procedures and publication decisions will be achieved using the widely used Editorial Manager™ software platform.

In an already overcrowded field of almost 50,000 academic journals [8], how will the Journal grow its academic profile, societal impact, and global popularity? Based on the current trends in academics and publishing, the Journal has taken bold, unprecedented steps to distinguish itself from all potential competitors. *First*, it is uniquely positioned to publish and amalgamate all areas of human knowledge, ushering a futuristic approach wherein the artificial and archaic boundaries between different academic disciplines continue to get blurred and/or entirely erased [9]. Publications resulting from outside-the-box thinking, with high-quality, transdisciplinary, innovative research will find a suitable home in the pages of this Journal.

Second, this Journal is the first to decouple the growing bonds between publishing and commercial interests. The Journal does not impose charges of any kind on authors, contributors, reviewers, editors, subscribers, or non-subscribers accessing this journal. One may question the Journal's sustainability and competitive edge against the established journals, motivated by commercial interests and owned by profitable publishing houses. We, however, have chosen the path less travelled and propose a different way to share knowledge without the limiting constraints of monetary transactions. Thus, the Journal aims to level the playing field for those who cannot pay to publish their research through traditional means, thus providing a respected, peer-reviewed platform for academic excellence and innovation hidden deep within the resource-limited universities or other settings.

Third, the Journal distinguishes itself through the unique profile of its Editorial Board Members, each one with authenticated academic credentials, irrefutable integrity, a societal focus, and esteemed standing within their own areas of expertise. The diverse Editorial Board and support staff of this Journal have made profound commitments to equity, diversity, and inclusivity in all its functions; quality and human-centeredness in its policies, procedures, and decision-making frameworks; with honesty and transparency in all its dealings – thereby positioning the Journal for future growth and success.

Last, but not least, a brief word about this journal's name. *Awareness* exists at various levels, from the superficial to the sublime. At one level, it signifies the broad purpose of this journal – to promote the awareness of high-quality, multidisciplinary research in all areas of human knowledge. Conceptually, "knowledge" implies the knower and the known, together with the active process of gaining this knowledge which connects the subject with its object. "Awareness" transcends this apparent distinction between the knower and the known because it exists beyond thought, word, and deed. *Awareness* also transcends the thought-based, rationale-driven, but artificial boundaries between disciplines, and therefore, this journal will receive and review work from all areas of conscious human endeavour. When the notion of 'I am' arises in pure undifferentiated consciousness, that notion itself is the person, an individual (the *jiva*). *Awareness* transcends these aberrations in consciousness that are generally perceived as 'the other', and so the journal does not endorse any transactional motives of selfish gain from its stakeholders or subscribers. Awareness works equally and equitably for the benefit of all, inclusive of all humans and other beings on this planet, the planet and its environs, all schools, colleges, or other research institutions, located in all countries and their subdivisions. We implore you to awaken to this journal's potential and help us usher in a new era of academic publishing.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed during this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

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Essay

Theorizing a Humanizing Pedagogy of Love

¹Sarina Chugani Molina, EdD¹University of San Diego, United States of America

Abstract: Historically, in many parts of the world, the roots of education were grounded in spirituality and wholeness. The enchanting pull of digital technologies and materialistic endeavors has resulted in higher levels of depression, anxiety, and risky behaviors amongst our young people. This review of the literature theorizes a pedagogy of love, which in essence, is a return to the roots of education grounded in the nurturing of wholeness in every child. The literature suggests that a pedagogy of love involves creating learning environments that centers the students, leverages their cultural, linguistic, and spiritual backgrounds and talents, prioritizes care, connection, and empathy that contributes to student sense of belonging, empowerment, and overall sense of well-being. In addition, a pedagogy of love stipulates a sense of criticality that seeks to promote equity and justice by removing systemic barriers and obstacles to student learning and thriving in schools and in society. This article proposes a humanizing pedagogy of love, grounded in integral and critically conscious education, to once again, nurture the wholeness in our youth as we work towards collective healing and well-being.

Keywords: pedagogy of love; spirituality, empathy; critical consciousness; mental health

Corresponding Author: Dr. Sarina Chugani Molina, Email ID: sarina@sandiego.edu

1. Introduction

Citation: Molina SC. *Awareness: Newer Horizons in Human Excellence*, 1 (1): 30-40..

Academic Editor: KJS Anand.

Received: 12-29-2023

Revised: 01-02-2024

Accepted: 01-03-2024



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The Centers for Disease Control and Prevention (2021) documented an upward trend in persistent feelings of sadness and hopelessness amongst 42% of youth with 22% contemplating suicide [1] (p. 58). According to the World Health Organization (2021), 1 in 7 adolescents experience mental health conditions [2]. Most recently, the World Health Organization (2023), reported that approximately 280 million people in the world suffer from depression [3]. Project Hope cautions us that mental health issues often begin at the early stages of life with over half beginning before the age of 14. Young people living through conflict are especially vulnerable and prone to mental health conditions [4].

A substantial body of research links digital media use including social media to mental health issues in children and adolescents. This evidence led the U.S. Surgeon General, Dr. Vivek Murthy, to issue an advisory in June 2023 on the potential harm of social media use on “youth mental health” [5]. Twenge & Campbell (2019) found that the use of digital media such as smartphones, social media, gaming, or simply being online, for example, is linked to lower psychological well-being among adolescents in two countries, based on three large surveys (n = 221,096) [6]. Those using digital media less than an hour a day were far better off in terms of mental health than moderate users and especially heavy users who use digital media five or more hours a day [6].

The likely impacts of digital media use on the mental health of children and adolescents call us to question our approach not only to parenting, but education as a whole.

In addition, researchers have found links “between materialism and mental health problems such as anxiety and depression, use of psychoactive substances such as alcohol and drugs, and egoistic attitudes and behaviors” [7]. Trzcińska et al. (2023) cite multiple studies that show a progressive decline in emotional well-being in our adolescents and children at younger and younger ages, which is cause for alarm.

This review of the literature theorizes a pedagogy of love, which in essence, is a return to the roots of education grounded in the nurturing of wholeness in every child. The literature suggests that a pedagogy of love involves creating a learning environment that centers the students, leverages their cultural, linguistic, and spiritual backgrounds and talents, prioritizes care, connection, and empathy, that contributes to a student's sense of belonging, empowerment, and sense of well-being. In addition, a pedagogy of love stipulates a sense of criticality that seeks to promote equity and justice by removing systemic barriers and obstacles to student learning and thriving in schools and in society.

2. Pedagogy of Love

Undoubtedly, it is only through the power of such love that teachers can embrace a revolutionary pedagogy and remain uncompromisingly committed to the restoration of our humanity [8] (Dardar, 2002, p. 148)

A pedagogy of love infuses both integral and critically conscious education. Integral education attends to the whole child, not only at the intellectual level, but at the socio-emotional and relational levels. Conscious education takes into consideration the historical, political, social, economic, community, and individual contexts that influence how students experience the world around them. Oftentimes, these contexts shape the ways in which students are centered or marginalized in educational spaces. Becoming a conscious educator entails the ability to become aware of and work towards transforming one's own prejudices and biases and becoming advocates for equity against systems of power that continue to oppress, disenfranchise, and divide.

2.1. Integral Education

There are many schools that have returned to nurturing the innate goodness in our children. Moving from a focus on academic excellence or knowledge production for material gain, holistic education focuses on six areas that have the whole child at the center whereby each naturally leads to academic excellence. These areas include: spiritual/moral development, social-emotional development, appreciation of arts and culture, physical fitness, values-based education, and care for the environment. For the remainder of this discussion, we will focus on three areas that have an increasing presence in the literature, namely, empathy, love, compassion, and spirituality that contribute to the holistic development of the child.

2.1.1. Empathy

Brené Brown (2012), renowned researcher on empathy and author of “Daring Greatly: How the Courage to be Vulnerable Transforms the Way We Live, Love, Parent, and Lead” emphasizes that “*Empathy is a strange and powerful thing. There is no script. There is no right way or wrong way to do it. It's simply listening, holding space, withholding judgment, emotionally connecting, and communicating that incredibly healing message of “you're not alone”*” [9] (p.81). The Dalai Lama extends this further and elucidates a broader perspective on empathy within the concept of compassion. One of the Dalai Lama's global initiatives that builds on empathy and compassion is Social, Emotional and Ethical or SEE Learning®. Launched in 2019, SEE Learning has reached classrooms in over 40 countries so far, enriching those educational systems [10]. The Dalai Lama states, “*A compassionate attitude helps you communicate more easily with your fellow human beings. As a result, you make more genuine friends and the atmosphere around you is more positive, which gives you greater inner strength. This inner strength helps you spontaneously concern yourself with others, instead of thinking only about yourself*” [11]. In essence, these thought leaders offer interconnected viewpoints on empathy. Whereas Brown emphasizes the importance of listening and emotional support, the Dalai Lama emphasizes compassion as a comprehensive framework for empathy, selfless action, and engagement with others. Together, their insights shed light on the multifaceted nature of empathy and its potential to create a more empathetic and interconnected world.

Empathy is one of five competencies within the framework of Emotional Intelligence, coined by Michael Beldoch in 1964 in his article titled *Sensitivity to Expression of Emotional Meaning in Three Modes of Communication* [12] and popularized by Daniel Goleman in his book *Emotional Intelligence* in 1995 [13]. Whereas IQ or intelligence was historically given prominence in schools and society in the past, the notion of emotional intelligence has been elevated in more recent times, whereby research suggests that 67% of the success of top performance is not intelligence or expertise, but emotional competencies [14]. For leaders, this increases to 90% with only 10% of their success dependent on their intelligence. The five competencies of emotional intelligence collectively contribute to building and maintaining healthy relationships, making sound decisions, and effectively managing oneself and others in various personal and professional settings. Developing and honing these competencies can lead to greater emotional well-being, improved communication, and enhanced overall success and satisfaction in life. The competencies are defined as follows:

- *Self-awareness*: Self-awareness is the ability to recognize and understand one's own emotions, strengths, weaknesses, values, and beliefs. It involves being in tune with our own feelings, thoughts, and motivations, and having a clear understanding of how they impact our behavior and interactions with others.
- *Self-regulation*: Self-regulation refers to the ability to manage and control our emotions, impulses, and behaviors. It involves exercising restraint, managing stress effectively, and adapting to changing circumstances without becoming overwhelmed. Self-regulation allows us to think before acting and make thoughtful decisions rather than being driven solely by our emotions.
- *Motivation*: Motivation refers to the drive and enthusiasm to achieve personal and professional goals. It involves setting high standards for oneself, having a sense of purpose, and being resilient in the face of challenges. Motivated individuals are passionate, proactive, and strive for continuous improvement.
- *Social skills*: Social skills encompass the ability to build and maintain positive relationships with others. It includes effective communication, active listening, conflict resolution, collaboration, and the ability to work well in teams. Having strong social skills enables us to navigate social situations, influence others positively, and establish connections based on trust and mutual respect.
- *Empathy*: Empathy is the capacity to understand and share the emotions, perspectives, and experiences of others. It involves being able to put ourselves in someone else's shoes, listen attentively, and respond with genuine care and concern. Empathy fosters understanding, compassion, and supportive relationships, and it plays a crucial role in effective communication and conflict resolution [14].

Research shows that children thrive both academically and emotionally in classrooms that foster and nurture empathy. Daniel Goleman and Peter Senge outline three kinds of empathy that students need for success at work and in life. These include cognitive empathy, emotional empathy and empathic concern. They define each as follows: "(1) *Cognitive empathy* is understanding how people see the world and think about it; (2) *Emotional empathy* is being able to sense what a person feels; and (3) *Empathic concern* is our ability to tune in and stop to help" [15].

A research study conducted in 2021 in the field of nursing entitled, *The Relationship between Empathy and Altruistic Motivations in Nursing Studies: A Multi-method Study*, found that high empathy scores were positively associated with altruistic motivational factors [16]. Felix Warneken, a professor in developmental psychology who studies cooperation and altruism in children, demonstrated through his research that children are naturally altruistic, which means that they care for the welfare of others selflessly. In his study, even when a child is happily playing, they stop what they are doing to assist others, which is a mark of putting others' interest before their own self-interest [17]. Given this natural empathy and altruistic motivations in children, it begs the question: What is it in the environment that makes children move towards self-interest and how can we once again, bring forth from within them, what already exists? Now, let us take a closer look at the resurgence of literature in recent years on the role of love, compassion, and spirituality in promoting student overall well-being.

2.1.2. Love and Compassion

In her TED talk, Dr. Shefali Tsabary (2010), a research psychologist in the area of conscious parenting describes the effect of parenting relationships on children's neurobiology. She demonstrates the impact of love on the development of

a child's brain through brain imaging of three-year old children. She states that when a child grows up in a loving home, it contributes to a healthy development of the brain. However, when a child is raised in a home with extreme neglect and devoid of love, the brain does not fully develop and is much smaller in comparison. She found that these children often grow up to have addictions and relational challenges [18].

The HeartMath Institute has found that the heart's magnetic field not only permeates every cell within us, but also extends out from us in all directions and can be measured. In his work with Syrian Refugee children in Lebanon, Kam-Almaz from HeartMath Institute provided a holistic assessment and compassionate care to the children who were suffering from urinary control as a result of trauma, and through connecting them with their heart center, he found that 85% stopped having urinary incontinence [19]. In another experiment conducted by the institute with a boy and his dog, they show rhythmic patterns of the heart fluctuating when there is separation and then coming together in synchronicity when there is love and connection [20].

These studies show that developing relationships with students built on love and connection becomes significantly more important for teachers in the classroom, particularly when there is lack of safety and security in the students' homes. In addition, it may also be important to support students in self-regulation practices to help them connect with their heart center to promote inner calm in times of conflict or turmoil. This does entail, however, the teachers' commitment to their own inner, self-regulation, and mindfulness practices in order to model this for their students.

Next, we turn to a discussion on spirituality and its relationship to lower rates of depression, substance use and abuse, or engagement with risky behaviors for youth particularly in the second decade of their lives.

2.1.3. Spirituality

With the separation of church and state, the use of spirituality or religion has been met with a sense of wariness. As such, it is important to first define what is meant by spirituality within the context of this article. In his book *The Secret Spiritual World of Children*, Tobin Hart (2003) defines religion as a systematized approach to spiritual growth formed around doctrines and standards of behavior, generally inspired by spiritual insight... and developed to spread through teachings, rituals, values, and rules of conduct [21] (*ibid.*, p. 8). Spiritual, he says,

*...naturally pertains to spirit, that unquantifiable force, the mystery that animates all things and of which all things are composed. There is no separating us from it. Any aspect of this life contains an essence of the whole, just as any of our cells contain the code for our whole form; spiritual moments are direct, personal, and often have the effect if only for a moment, of waking us up and expanding our understanding of who we are and what is our place in the universe [21] (*ibid.*, pp. 7-8).*

Maria Montessori, a scientist, physician, and educator, believed that it is important to come together to respect and support the inner workings of children as they interact and engage with the wonders of the world and their inner lives. She believed that all children have an inner guide of their own, and that the education capable of saving humanity involves the spiritual unfoldment and enhancement of the values inherent in each child. The role of teachers is to walk together with the children on this path of life, she says, for all things are part of the universe and are connected with each other to form one whole unity.

Dr. Lisa Miller, author of *The Spiritual Child: The New Science on Parenting for Health and Lifelong Thriving* [22] and *The Awakened Brain: The New Science of Spirituality and our Quest for an Inspired Life* [23], and leading scientist conducting research connecting brain science, spirituality and psychology of the mind, found that particularly in the first two decades of our lives, our inborn natural spirituality is foundational to our mental health and well-being. Miller (2016) defines spirituality as some form of transcendent relationship – a belief in a higher power, be it God, be it love, be it the universe, which can be expressed through prayer or a feeling of oneness with the universe [22] (p. 25). In the research conducted with her team of scientists, she found that children with a strong spiritual connection tended to fair well with positive emotions and optimism, and those without a strong spiritual connection, particularly in the second decade of their lives, experienced “high rates of depression, substance use and abuse, and conduct problems involving risk-taking” [23]. She further elaborates,

I've discovered that the awakened brain is both inherent to our physiology and invaluable to our health and functioning. The awakened brain includes a set of innate perceptual capacities that exist in every person through which we experience love and connection, unity, and a sense of guidance from the dialogue with life. And when we engage these perceptual capacities - when we make full use of how we're built - our brains become structurally healthier and better connected, and we access unsurpassed psychological benefits: less depression, anxiety, and substance abuse; and more positive psychological traits such as grit, resilience, optimism, tenacity, and creativity" [23] (Miller, 2021, p. 9).

Miller's study with associates, on the *Neuroanatomical Correlates of Religiosity and Spirituality: A Study in Adults at High and Low Familial Risk for Depression*, found that for those who consider religion or spirituality as personally important to them, areas of their brains thickened and this thickening was related to higher emotional satisfaction and mental health. Therefore, when we engage our spirituality or find that spirituality or religion are important to us, our brain cortex becomes healthier and more resistant to depressive states [24] (p.133).

This body of research suggests that a teacher's awareness of the students' religions, spirituality, and/or indigenous wisdom traditions contributes to a better understanding and relational experiences with students where their beliefs and values are honored, rather than sidelined. As research begins to uncover the importance of attending to students' inner lives in order to nurture their overall well-being, teachers must also be conscious of the ways in which systemic barriers can negatively impact a students' sense of well-being.

The next section elaborates on the construct of conscious education, specifically critically conscious education and how this type of critical consciousness is required for teachers to enact change in their students' lived experiences and circumstances.

2.2 Conscious Education

Conscious educators take into consideration the historical, political, social, economic, community, and individual contexts that influence the experiences and achievements of students in their classroom. Oftentimes, these contexts shape the ways in which students are centered or marginalized in educational spaces. Critical consciousness entails the ability to become aware of and work towards transforming one's own prejudices and biases and then become advocates for equity against systems of power that continue to oppress, disenfranchise, and divide.

Darling-Hammond suggests that "Developing the ability to see beyond one's perspective, to put oneself in the shoes of the learner, and to understand the meaning of that experience in terms of learning, is perhaps the most important role of universities in the preparation of teachers" [25] (p. 170). Honoring students' funds of knowledge, their experiences, their backgrounds, and the literacies they bring into the classroom from an asset-based lens [26-31] and leveraging the individual and community wealth that students bring into educational spaces, will enhance learning opportunities for them. Yosso describes this as community cultural wealth including linguistic capital, cultural capital, familial capital, social capital, amongst others [32].

For conscious educators, Ramasubramanian et al. propose a framework that encourages teachers to: (1) Realize that dominant ideologies are embedded in our educational systems, (2) Recognize the long-term effects of systemic trauma on learners from aggrieved communities, (3) Respond to trauma by emphasizing safety, trust, collaboration, peer network, agency, and voice within learning environments, (4) Resist retraumatization within learning environments, (5) Replace egalitarianism with equity-mindedness and (6) Reframe deficit ideology with an asset-based lens to learners [33].

Dominant ideologies can include languages adopted as a medium of instruction, social class that is privileged in the curriculum, and cultural mindsets that influence how boundaries and limits are put on children based on their gender, socio-economic status, race, etc. It is important for conscious educators to be aware of the historical, generational, and individual traumas that students may bring to the classroom and create a warm and loving, learning environment for

them. Being sensitive to the possible traumas they bring and resisting retraumatizing students through particular topics or activities would be important. Truly understanding that opportunities are not equal for all people and working towards equity is one of the ways in which conscious educators can begin to raise awareness and transform systems of oppression.

From time to time, deeply committed teachers can experience moments of despair as they struggle to challenge and oppose traditional methods, relationships, and structures within schools that oppress students, parents, and teachers alike. During these moments, it is helpful for teachers to stop and consciously reconnect with the historical nature of their work and the larger social struggle for economic democracy and social justice around the world [8] (Dardar, 2002, p. 64)

In other words, critically conscious education is a form of problem-posing education, where teachers recognize manifold ways in which inequities present themselves within political, economic, social, and cultural systems that then influence educational systems. The next two sections provide examples on the role of dominant language ideologies and gender disparities particularly in educational spaces that perpetuate social inequality in order to illustrate what problem-posing education can look like.

2.2.1. Problem-Posing Example: Language

In many schools where dominant languages are used as a medium of instruction, student home languages, literacies, and cultural ways of being are often seen as “deficiencies to be overcome in learning” [31]. One of the outcomes of colonialism was the promotion and adoption of a national language as a unification strategy. The promotion of a national language was given priority over heritage languages, while at the same time, languages such as English were believed to be a *lingua franca* that would improve opportunities for economic mobility. As English and other dominant languages gained political and social capital, heritage languages suffered through devaluation, endangerment, and ultimately “linguicide” or linguistic genocide as Skutnab-Kangas articulated - this, she sees as a “human rights issue” [34].

The colonizers spend centuries trying to impose their language. The colonized people were told either verbally or through message systems inherent in the colonial structure that they did not possess effective cultural instruments with which to express themselves. This language profile imposed by the colonizers eventually convinced the people that their language was in fact a corrupt and inferior system unworthy of true educational status [8] (Freire & Machado, cited in Dardar, 2002, p. 118)

Milligan et al. argue that when a dominant language is used as a medium of instruction and children are not proficient in this language, this gap in language proficiency could lead to “limited access to schooling, high repetition, failure, and dropout rates; poor quality of education and low learner self-esteem” [35] (p. 118). Kosonen [36] and Benson [37] both found that the use of dominant languages as the medium of instruction resulted in significant gaps in educational access and attainment between the rich and poor, elite and marginalized, and males and females [36-37]. “Three groups most affected by injustices in language policy and planning in education are women and girls, the poor, and groups with languages not represented in formal structures” [38].

Recent research [39] confirms that the home language or heritage language facilitates literacy in the second language [40-42]. In addition, when a student’s home languages and cultures are valued in educational spaces, students develop a higher sense of self-esteem, higher self-confidence, and higher aspirations in schooling and in life [37].

Despite such findings and “the importance of heritage language or mother-tongue instruction having been recognized and re-emphasized (UNESCO, 1953, 2017), the force of globalization and English as the linguistic capital necessary to participate in systems of economic, political, and social power, has resulted in the loss and death of many heritage languages” [39]. As such, teachers should leverage the various forms of capital [29] that students bring into the classroom through asset-based pedagogies.

2.2.2. Problem-Posing Example: Gender

In many parts of the world, a girl child may not have access to education or may have been born in paternalistic cultures where gender disparities are entrenched. Many nonprofit organizations have garnered this sense of criticality in their work by providing opportunities for girls to receive an education to transform their lives.

Goats are assets and girls are liabilities

Safeena Husain (2013) is the founder and board member at Educate Girls, an organization that aims to bridge the gender gap for education in India and promotes a change in the narrative of goats as assets and girls as liabilities. She shares the following statistics for girls out of school in India:

[A girl out of school] is 70% more likely to become a child bride, which means that she would be married before the legal age. There is a real 15% chance that she will be married before the age of 11...If she doesn't go to school, she will in a lifetime, earn less than her counterparts...She's more likely to be trafficked, be in domestic violence situations, and there is only a 15% chance that she will ever learn how to read. The odds against [her] are immense. Only 1 in a 100 girls in rural India even makes it to class 12...For each year she stays in school, her family income goes up by 10-15%...Her marriage will be delayed...She would be 40% more likely to immunize her children...Being an educated mother, she is 500 times more likely to educate her own children. It is a cycle we need to break in our own lifetime [43].

Much of this work entails going into communities and transforming limiting beliefs for girls. It is truly through transforming one mind at a time that cultures, communities, and societies can gradually shift, but this requires building trusting relationships through family, school, and community partnerships.

In this way, conscious educators “develop their power to perceive critically the way they exist in the world with which and in which they find themselves” and “come to see the world not as a static reality, but as a reality in process, in transformation” [44]. As such, teachers must engage in continual reflection and introspection as they transform their own beliefs and reconstruct knowledge as they work towards justice and equity in their classrooms [45] and in the communities in which they serve where visible and invisible hierarchical systems such as caste systems might exist. Equipped with this knowledge, teachers can encourage students to think about ways in which they can transform their own state or status, and their own limiting beliefs about themselves. Styslinger et al. argue that critically conscious educators “teach by raising student consciousness and then trusting that students ‘will feel increasingly challenged and obliged to respond’ to the inequities and injustices they come to recognize and realize” [46] and equips them with “a sense of agency and capacity to interrupt and change oppressive patterns in themselves and in the world which surrounds them” [46] (p. 9). Rather than a banking model of education [44], where teachers transmit knowledge into the minds of the students, this approach prepares students to take the knowledge and participate in it creatively and responsibly for their own transformation [46].

As described above, conscious education centers the co-creation of knowledge between teachers, students, and their families and communities within historical, political, economic, and social systems in which they operate, and works towards developing thoughtful and compassionate students who will continue to strive to work towards the transformation of themselves and their communities.

3. Concluding Thoughts and Future Directions

“It is impossible to teach without the courage to love, without the courage to try a thousand times before giving-in. In short, it is impossible to teach without a...capacity to love” - [47](Freire, 1998, p. 3)

A humanizing pedagogy of love attends to both the internal lives of the students and the external circumstances that influence the hidden curriculum – the how and what is taught and to whom. Relationships are at the core of happiness

as reiterated by Harvard professor, Arthur Brooks and television icon, Oprah Winfrey (2023), who share the science of happiness in their new book entitled, *Build the Life You Want: The Art and Science of Getting Happier*, building upon a longitudinal study on adult development by Harvard researchers. The four foundational pillars of happiness, they write, include family, friends, faith, and work as service [48]. As elucidated in this article, empathy, love, and compassion are at the heart of authentic relationships; one's faith, be it a particular religion, or spiritual, transcendent connection is integral to one's sense of well-being; and lastly, finding meaning and purpose in our life and work in the spirit of service is what can heal the hearts of our children and youth today for a better tomorrow.

A humanizing education is the path through which men & women can become conscious about their presence in the world. The way they act and think when they develop all of their capacities, taking into consideration their needs, but also the needs and aspirations of others [49] (Freire & Betto, 1985, pp. 14-15 cited in Dardar, 2011, p. 498).

The work of a teacher is indeed a work of service. To do this effectively, a teacher has to attend to their own transformation first through reflection of their own biases and tendencies, their privileges or lack thereof, and to understand the ways in which these manifest in their relationships, pedagogies, and practices. In addition, understanding their students, their backgrounds, their histories, and the interplay of cultural, social, and political influences within the educational contexts in which they situate themselves, can contribute to tailored interventions that can support teachers in unlocking each of their students' unique potential.

Why is this important?

Freire exposed how even well-meaning teachers, through their lack of critical moral leadership, actually participate in disabling the heart, minds, and bodies of their students – an act that disconnects these students from the personal and social motivation required to transform their world and themselves [49] (Dardar, 2011 p. 498).

Future studies can report on short-term and longitudinal qualitative and quantitative research that delves deeper into the impact of each of the components of integral and critically conscious education on student overall well-being, empowerment, and community advocacy for equity and justice to inform the evolving theorization of a humanizing pedagogy of love.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed during this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

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Brief Report

Leading Causes of Life in Medicine: Pilot Studies

Teresa F. Cutts^{1,2} and Gary R. Gunderson^{1,2,3}

¹Department of Social Sciences and Health Policy, Division of Public Health Sciences, Wake Forest School of Medicine, Medical Center Boulevard, Winston Salem, NC 27157

²Stakeholder Health, 502 Tanners Park Court, Winston Salem, North Carolina 27101

³Wake Forest University School of Divinity, 1834 Wake Forest Road, Winston Salem, NC 27106

Abstract: The five Leading Causes of Life (connection, coherence, agency, intergenerativity or blessing, and hope) framework has been piloted in medical settings, including health system employee orientation, integrative primary care settings, and executive physicals for healthcare leaders and clergy. The Leading Causes of Life were assessed in several hundred persons and integrated into in primary care and clergy health integrative medicine care plans, as well as within an executive physical model called “Life of Leaders”, conducted with 130 persons from 2007-2013 in Memphis, TN. More secular and younger primary care patients reported that the assessment and focus on Leading Causes of Life vs. pathology was empowering but reported less hope and agency. Clergy/chaplain populations reported that this framework opened up rich dialogue for future health discussions, while reporting less coherence than their secular counterparts. Leading Causes of Life with the spiritual- and asset-based assessment within the executive physical model was useful as an every 3-year adjunct to typical annual physicals and particularly helpful during transition periods in leaders’ lives (e.g., upcoming job sabbatical, promotion, retirement). Use of the Leading Causes of Life framework in medical settings may be useful in moving away from the traditional, pathology-based models of care and deserves more exploration in all healthcare settings.

Citation: Cutts TF, Gunderson GF.

Awareness: Newer Horizons in Human Excellence, 1 (1): 41-48.

Academic Editor: SP Setty.

Received: 12-28-2023

Revised: 01-03-2024

Accepted: 01-04-2024

Keywords: asset-based, executive physical, health systems, integrative medicine, leading causes of life, positive psychology, positive deviancy

Abbreviations: Leading Causes of Life (LCL), Leading Causes of Life-Initiative (LCL-I), Post-Traumatic Growth (PTG)

Corresponding Author: Dr. Teresa Cutts; Email ID: cutts02@gmail.com



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1. Introduction

Leading causes of life (LCL) is an asset-based framework [1] that moves away from traditional, pathology-based medicine traditionally focused on the “leading causes of death” [2] to instead focusing on what enhances or optimizes life. The LCL framework is related to positive deviancy, which promotes harvesting and scaling community wisdom to find solutions [3,4]. Grounded in social complexity theory, LCL also resonates with flourishing and resiliency models [5], particularly positive psychology [6], which is the scientific study of what goes right in life. The five “causes” include connection, coherence, blessing or intergenerativity and hope. A more in-depth review of the causes can be found elsewhere [1,7] but are reviewed briefly here.

Connection refers to how humans are social creatures that need relationships to support and optimize their health. Connection is vital for humans from early infancy

in terms of just basic touch, as evidenced by early studies of orphans, who failed to thrive and often died prematurely when not touched or held regularly [8]. More recent studies of both animals and humans indicate that touch can decrease anxiety, depression, muscle tension, heart rate, and promote healing after stroke [9]. Human beings find life through complex social relationships and connections to one another, building communities of various kinds that enable us to adapt to changing threats and opportunities [10].

Coherence refers to how persons make sense of their own narrative or story. Actively crafting and living into that personal story is evidenced in the post-traumatic growth syndrome or PTG, whereby persons grow more resilient or stronger after trauma [11]. Coherence defines how we make sense of life, how we order an otherwise overwhelming confusion from the experiences of nature and of ourselves in seeing our life journey as intelligible and neither simply random nor victim to inexplicable forces [10].

Agency refers to the human capacity to choose to do. This is illustrated in the works of Bandura [12], whose work on self-efficacy suggested that a belief that persons can change their lives offers a sense of control over any circumstances, often resulting in more resiliency and proactive behavior. The capacity to act intentionally in the world, both our creative freedom and a moral awareness of our responsibility for what we do and why, marks our human spirit and is a central cause of life, that is unalienable and universal [10].

Blessing or inter-generativity refers to the relationship with those closest to us, including our ancestors, parents, children, and future generations. This cause is related to the field of psycho-neuro-immunology or how our immune system is impacted by our attitudes, beliefs, thoughts, and emotions, highly tied to encounters with others, and can impact physical and mental wellness [13]. Visits with others can decrease loneliness, depression and result in improved immune system functioning for both parties [14]. Human lives are blessed and nurtured by those who come before and after us, we are encouraged, strengthened, enlivened and better able to shape our own lives, to make vital choices. Active blessing means bestowing upon another approval or praise, while affirming their sacredness as a person and wishing them well [10].

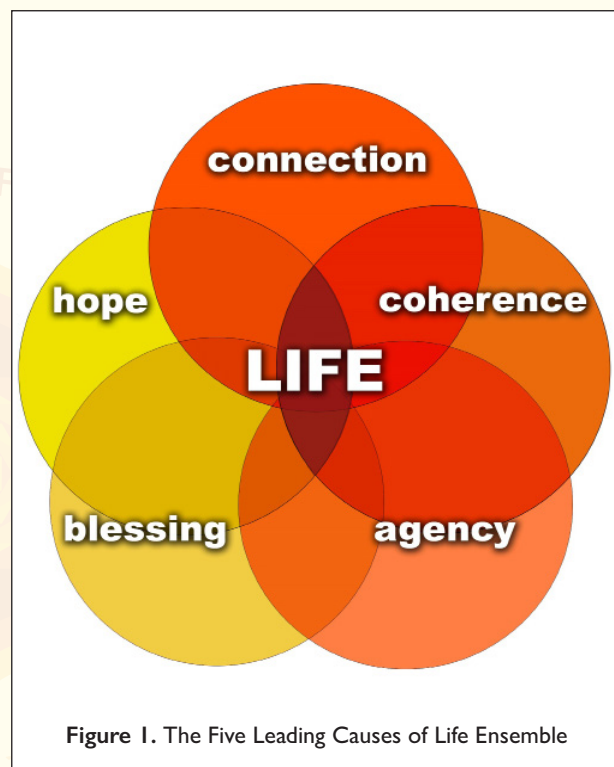


Figure 1. The Five Leading Causes of Life Ensemble

Lastly, **hope** refers to a positive orientation toward the future, even a “memory of the future” [15] and can highly impact medical outcomes. Hope is not simply optimism or wishful thinking but focuses on the human capacity to imagine a different, healthier future and to find the energy to do something to make that happen [10]. Dozens of studies reflect better cancer, cardiac, post-surgical outcomes, as well as decreased levels of anxiety and depression in those with higher levels of hope [16]. Countless studies also have linked improved outcomes in pain management and general immune system functioning in persons who demonstrate higher levels of hope [17].

The five causes are not designed to be independent; rather they work together as an ensemble and have considerable and intentional overlap in terms of domains of each cause [10]. The focus in using the LCL framework and early tools described below was to work with and build upon the asset of each cause that a person possessed, not focus on what was lacking. Figure 1 visually presents the 5 intentionally interdependent Leading Causes of Life.

2. Materials and Methods

The LCL framework was piloted across medical and other settings from 2007-2013.

Health System Setting: Orientation and Leadership Training

The first use of the LCL framework was to introduce it as part of each new employee orientation at the Methodist Le Bonheur Healthcare (MLH) system. A 30-minute introduction to the five causes were shared from Faith & Health staff on

the first day of work for individuals at all levels of the organization (e.g., from executives, physicians, nurses to front-line workers, such as environmental and food service workers and security).

Additionally, every quarter, the top 500 leaders of the health system were trained in a three-hour, comprehensive use of the LCL framework in their various work settings.

Lastly, since MLH was owned by the three local state United Methodist Church Conferences (Memphis, Arkansas, Mississippi), a two-day conference on LCL was offered to each conference from 2008-2010. This two-day conference format was designed for large lecture groups in which the general framework of LCL was presented by Dr. Gary Gunderson in extended dialogue. Next, Rev. Larry Pray (co-author of the LCL book) presented ways to infuse the Leading Causes of Life into pastoral settings/work and lead the group in several small group exercises to teach these strategies more effectively. A unique aspect of this interactive teaching was the “five-course meal” format that engaged small dinner groups around discussion of each of the five causes. Lastly, Dr. Teresa Cutts presented the high-level health science or “found science” under-girding this work, integrated into clergy and congregational contexts. This conference offering fit well into a state or regional-level denominational leadership meeting and was an excellent awareness level introduction to the Leading Causes of Life framework for broader clergy leadership. Particularly, with Bishop leadership at the initial and ending services, this introductory conference served as a springboard to engage top and middle clergy leaders in understanding and using the Leading Causes of Life framework in their ministry.

Primary Care Integrative Medicine Setting

The creation and development of a brief LCL survey for individuals was then piloted at our integrative, spiritually based primary care clinic, Harbor of Health, in Memphis. Survey development and test construction logic was not psychometrically sound in terms of independent domains. As mentioned above, the five causes intentionally overlap in domains assessed and the survey was designed to stimulate conversation about assets and life with patient-provider dyads or small groups, not measure singular cause factors.

Over a period of three months, patients consecutively presenting to this new clinic, focused on wellness and prevention, were offered the LCL survey as part of their medical intake process. This was in addition to the traditional Health Risk Appraisal, which again, focuses primarily on pathology. Ninety-eight percent (N=100) completed the survey. Two females declined to complete the full survey, as they did not wish to share their spiritual views. This cohort was young (mean age of 34.8 years of age) with 65% identifying as female and 35% as male.

Clergy Conference and Chaplaincy Setting

The LCL survey was offered to all participants of the three clergy conferences offered by the MLH system leaders from 2008-2010. Additionally all MLH chaplain and chaplain residents completed the survey over a two-year period, for a total of 400 persons completing the survey. To enhance our ability to capture survey findings, no personal health information or demographic data were captured on those completing the survey, but the general estimate (from conference leaders' report) was that average age of this cohort was in their late 50's and predominantly male.

Life of Leaders Executive Physical

Leading Causes of Life were integrated into a spiritually based Executive Physical that was developed by MLH and the Church Health Center in Memphis, TN. The process, called Life of Leaders, is described in depth elsewhere [18]. Approximately 130 clergy leaders (including Bishops and District Superintendents of the United Methodist Church) and other executives (Foundation presidents, magazine editors, etc.) experienced this two- and one-half day assessment, including dialogue and recommendations from health providers, as part of this leadership process from 2007-2013.

Life of Leaders was designed to focus on how life is a journey, not an event and how health issues and perception of these issues occur across the lifespan. It was developed to be an adjunct to regular wellness examinations, offered every 3 years or whenever a person desired a reset or revitalization, such as job sabbatical, promotion, transition, or retirement. In Memphis, it was intentionally hosted at a clinic and wellness center that catered to the underserved, to highlight the focus on integration of those with power and affluence with the “least of these.”

The program was team-based, with the physician working closely with a life practitioner (so named to down-play their role in behavioral health and focus more on assets than psychopathology), exercise physiologist and/or physical therapist and nutritionist. Cohorts of up to 12 participated in group meals, fellowship, and local musical events. Concierge

services were tailored to the needs/wishes of each participant, based on extensive pre-work assessments (LCL survey, Values in Action Strengths Survey, brief Myers Briggs, Your Health Journey Narrative, Health Risk Appraisal or HRA; also most recent annual physical findings from the last medical checkup). Specifically, the Your Health Journey narrative was crafted as the antithesis of the “traditional History and Physical” assessed in medical encounters, as it tapped into assets and concerns across the person’s lifespan and family history. Services offered included specialty consults (e.g., sleep, pain management) and integrative medicine treatments (e.g., Tai’chi, acupuncture, acupressure, Pilates, aromatherapy, massage). Extra time (90 minutes) was afforded with both the physician and life practitioner, to allow the participant to relax into the space and share more of their concerns/thoughts, both on Day 1 of assessment and Day 2 of Reporting Back/Recommendations. Copies of all medical records/reports were given in full form to each participant, to promote transparency, convenience, and to encourage sharing it with their local primary care provider upon returning to their home settings. See Table 1 for key components of the Life of Leaders leadership process.

Team-Based	Concierge	Extra Time	Pre-Work
Medical Provider, Life Practitioner, Nutritionist, Physical Therapist/Exercise Coach, Other Specialists as desired. Group music and meditation from local artists, meal and fellowship.	Tailored to individual needs/wishes for specialty consults (e.g., pain management or sleep) or treatments (e.g., massage, acupuncture, Pilates, aromatherapy) as requested on prework	Participant spends 90 minutes each with Medical Provider, Life Practitioner, Nutritionist and Exercise Coach on Day One; Also 90-minute Day Two report back with Medical Provider and Life Practitioner Team	Extensive pre-work packet completed two weeks before event with Myers Briggs, Positive Psychology surveys, Leading Causes of Life survey and Health Risk Appraisal and Your Health Journey Narrative assessments

Table 1. Key Components of the Life of Leaders Process

3. Results

3.1. Health System Orientation & Leadership Training

Introduction of LCL into all new employee orientation was rated as a highlight of and one of “most useful” aspect of those orientations by employees within the system. Anecdotal reports of novel use of the framework came from disparate hospital employees, some unexpected. For example, the supervisor of employees whose job was calling former patients to collect unpaid bills (admittedly an often unpleasant conversation for both parties) trained her staff on how to use LCL to approach their calls in a more affirming and positive manner. Also, the Dr. Gary Gunderson was invited to offer the keynote address on LCL to the state association of pathologists, to enhance their work.

In the MLH new employee, high level leadership and clergy conference LCL trainings, those exposed indicated that inserting LCL language alone served as an “intervention” to change patient-provider dialogue or even community-based conversations to be more proactive and less pessimistic.

3.2. Primary Care Integrative Medicine Clinic

At the Harbor of Health clinic, our younger, more secular group of patients reported lower levels of connection and agency, compared to clergy and chaplaincy cohorts. Correlations between lower agency and coherence scores were found on those patients who reported more headaches, GI disorders, substance use disorder, depression, and muscular skeletal pain on the HRA. Patients reported positive experiences in thinking through their strongest LCLs and being refreshed by being asked this question: “What is right with you?” by the primary care physician in the care plan development that incorporated both HRA and LCL findings.

3.3. Clergy Conference and Chaplaincy

This cohort demonstrated lower scores on coherence and higher scores on blessing and connection. Mixed scores were noted on hope. Cohort respondents liked the more positive LCL framework, particularly those who reported some degree of compassion fatigue or were struggling in their ministries. Most reported that they wished to have time to discuss these findings in small groups to further process and maximize the benefit of the framework. However, clergy often quickly moved to focus on how LCL could be used to assess congregational strengths, vs. keeping the focus on their individual findings. See Appendix A for a copy of the LCL survey for individuals.

3.4. Life of Leaders Executive Physical

Life of Leaders was conducted with N=130 persons, 75% persons identifying as males and 25% identifying as females. Mean age was 62 years. Early piloting of this process in 2007 with 18 UMC Bishops of the Duke Episcopal Leadership Foundation group revealed how potent this process of leadership engagement around life and faith and health could be. Anecdotal feedback from the original cohort held in 2007 included:

- Staff commitment and knowledge helped me move from focusing on the past to claiming the future: “I have been looking at my life as a rearview mirror view. This framework focuses me on what’s ahead in my future—positive Life.”
- The integrated provider teamwork and the way they communicated about my clinical findings to create a holistic report was great.
- The assets-based model was superb and supported my gifts and talents while showing me creative ways to use these to achieve optimal health.
- Your wonderful team successfully blended the best of an executive health examination with helpful support for self-care, spiritual nourishment, relaxation, and conversation.
- The experience was “Better than Mayo” (i.e., better than Mayo Clinic’s Executive Physical process) in its focus on Leading Causes of Life in very creative ways.
- True integration of mind/body/soul

Structured, anonymous evaluation was captured from the Life of Leaders participants via e-mail surveys within one month of the process. It revealed that 74.4% of the cohorts gave the highest rating of “Excellent”, with an overall response rate of 34%.

4. Discussion

These early pilot findings require further evaluation, refining of findings, and research of more specific hypotheses regarding the LCL framework and surveys than have been conducted to date. However, the almost universally positive response to the LCL framework, from health system employees as disparate as financial collector supervisors, pathologists, and janitorial staff, suggest that the continued use of LCL training within medical settings is merited and that the language framework itself is robust enough to be utilized across health systems, medical specialties and even clergy and chaplaincy populations. Likewise, the dialogue stimulated between providers and patients in a primary care setting, with the flip of asking “What is right with you?” vs. “What is wrong with you?”, much like the recommended *Awareness 2024*, Vol 1, Issue 1: Pages 33-38 37 resilience question of “What happened to you?” rather than “What is wrong with you?” also indicates the usefulness of LCL and argues for a broader implementation of the LCL framework.

As noted recently in JAMA [19], a shift in perspective is needed in medicine, moving away from pathology and death to health and well-being, exemplified by the Leading Causes of Life. As Dr. Philip Pizzo, the former Dean of Stanford School of Medicine and Founding Director of the Stanford Distinguished Careers Institute notes: “physicians and other clinicians [need to] think differently about how to support the longer lives of their patients, focusing on how to make them more

meaningful and functional and less attenuated by the morbidities that lead to medical, social, and financial dependency.” [19]. The Leading Causes of Life framework seems ideal for this purpose, thus meriting further utilization and research.

Funding: This research received no external funding.

Informed Consent and Institutional Review Board Statement: Standard informed consent was obtained for all patients described below seen in primary care and other clinical settings. In congregational, health system orientation and seminar settings, patient consent was waived due to participants being exposed to purely educational materials LCL. Formal institutional review board ethical approval for consent to participate was waived for all activities described above, as these offerings were part of health system quality improvement efforts of the Center of Excellence in Faith & Health at Methodist Le Bonheur Healthcare.

Acknowledgments: The authors wish to thank the staff and volunteers of the Harbor of Health clinic, Church Health Center, and the Faith & Health Division of Methodist Le Bonheur Healthcare, for piloting the LCL surveys, health system orientation/training, and running the Life of Leaders executive physicals.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

Please choose your best response to each question below. There are no right or wrong answers.

Table A1. Leading Causes of Life Survey-SF (Short Form)

1. I can think of at least five people who feel they can count on me if they need help or someone to talk to.	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
2. In the past year I have been able to make some choices that make a difference in the lives of those that live around me.	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
3. I am part of faith or service group that depends on me and would be missed if I dropped out.	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
4. On most days I experience meaningful connection to a loved one.	Strongly Disagree	Disagree	Neither agree nor Disagree	Agree	Strongly Agree
5. If I wanted to, I feel like I could change my job or where I live.	Strongly Disagree	Disagree	Neither agree nor Disagree	Agree	Strongly Agree
6. If we choose to do it, we could make a difference in the really big issues, such as hunger, the environment and poverty.	Strongly Disagree	Disagree	Neither agree nor Disagree	Agree	Strongly Agree
7. On most days I find something that makes me laugh.	Strongly Disagree	Disagree	Neither agree nor Disagree	Agree	Strongly Agree
8. I am able to talk to my loved ones about things that really matter.	Strongly Disagree	Disagree	Neither agree nor Disagree	Agree	Strongly Agree
9. On most days I am able to express my purpose in life through my work.	Strongly Disagree	Disagree	Neither agree nor Disagree	Agree	Strongly Agree
10. My parents are proud of me (or would be, if they were alive).	Strongly Disagree	Disagree	Neither agree nor Disagree	Agree	Strongly Agree

11. When I make mistakes, I am able to ask forgiveness from those I care about the most.	Strongly Disagree	Disagree	Neither agree nor Disagree	Agree	Strongly Agree
12. I think in some way that my life is making the world a better place for the next generation.	Strongly Disagree	Disagree	Neither agree nor Disagree	Agree	Strongly Agree
13. The things I value most will endure after I die.	Strongly Disagree	Disagree	Neither agree nor Disagree	Agree	Strongly Agree
14. When I think about the future of those I love, I am positive.	Strongly Disagree	Disagree	Neither agree nor Disagree	Agree	Strongly Agree
15. I can see where God is working in the world for good.	Strongly Disagree	Disagree	Neither agree nor Disagree	Agree	Strongly Agree

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Narrative Review

Approaches for Unraveling Complex Human Genetic Diseases

Nallur B. Ramachandra*, Chavadapur S. Srushti, Kommerahalli R. Meghana

Department of Studies in Genetics and Genomics, University of Mysore, Manasagangotri, Mysore, India.

Abstract: Human genetic diseases significantly burden the family and society. The key concern is understanding the diseases' etiology, prevention, treatment, and management. Even though there are many analytical methods and tools available, overall knowledge of these has yet to reach needy families. Here, we systematically narrated the methods and techniques such as pedigree analysis, the pattern of inheritance, cytogenetic analysis, next-generation sequencing, drug discovery, personalized genomic medicine and artificial intelligence employed to diagnose and treat genetic diseases, particularly complex diseases. These techniques help unravel the high-risk causal genes and their variants, further enabling drug discovery research groups and leading to personalized, targeted therapeutic interventions.

Keywords: Human Complex Genetic diseases, pedigree, inheritance pattern, cytogenetics, next-generation sequencing, drug discovery, genomic medicine.

Corresponding Author: Dr. N.B. Ramachandra; Email: ramachandra@genetics.uni-mysore.ac.in

Citation: Ramachandra NB, Srushti CS, Meghana KR. *Awareness: Newer Horizons in Human Excellence*, 1(1): 49-47.

Academic Editor: KJS Anand.

Received: 12-29-2023

Revised: 01-04-2024

Accepted: 01-06-2024



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1. Introduction

Genetics unravel the mysteries of life processes. One-sixth of the world's population suffers from various genetic disorders. Genetic diseases can be seen from birth to later in life [1]. The Indian population has enormous variability due to consanguineous marriages among different cultures, ethnic groups, and caste systems [2]. Thus, genetic disorders of varied inheritance patterns are not uncommon in India and other developing countries.

Studying the origin and mechanism of genetic diseases has become possible with recent scientific advancements. All the diseases studied may have at least one genetic component. Rare and complex diseases are responsible for significant morbidity and mortality, which pose a global threat. Population screening and investigating etiological factors at the phenomics and genomics levels help diagnose and prevent diseases through early intervention and follow-up counselling [3]. The present task is to unravel the genetic component of complex diseases.

2. Genetic diseases

Changes in the genetic material lead to the four main types of genetic diseases as described below [4].

2.1 Single-Gene diseases

Single-gene diseases are caused by a single defective gene in chromosomes with a predictable inheritance pattern. They can be either dominant or recessive. If the disease is dominantly inherited, it requires the presence of one defective copy of the gene from either parent to manifest, whereas recessive diseases require two copies of the affected genes, one from each parent. Currently, the Online Mendelian Inheritance in Man (OMIM) documents 4,434 disease genes that, when mutated, provide the underlying causal basis for 6,306 Mendelian disorders (<https://www.omim.org/statistics/geneMap>) (OMIM compendium, 2023) [5]. Examples include sickle cell anemia & phenylketonuria.

2.2 Chromosomal Abnormalities

Chromosome abnormalities are characterized by a structural or numerical alteration in single or multiple chromosomes, affecting the autosomes or, allosomes or both. Numerical aberrations include changes in the chromosome number, aneuploidy or whole set of chromosomes, euploidy. Structural aberrations include deletions, duplication, inversion and translocation of chromosomal segments [6, 7]. Examples include Down's syndrome and Prader-Willi syndrome.

2.3 Mitochondrial Diseases

Extranuclear DNA is present in the mitochondria of all eukaryotic cells. Mitochondrial diseases are caused by mitochondrial DNA variants, which are inherited maternally. Therefore, the mutations are transferred from mothers to all their offspring but never from the father. Defects in oxidative phosphorylation identify mitochondrial diseases. These are caused by the changes in mitochondrial and nuclear DNA [8]. Mitochondrial disease can vary in severity and penetrance due to heteroplasmy. Examples include Leber Hereditary Optic Neuropathy (LHON) and Leigh Syndrome.

2.4 Multifactorial Diseases

Multifactorial diseases are caused by the effects of more than one gene in combination with lifestyle and other environmental factors. This is the most frequent disease cluster in families without a clear inheritance pattern. Examples include Diabetes and Hypertension. The prevalence of chromosomal, single-gene and multifactorial diseases are 3.8, 20 and ~600, respectively [9]. The etiology of these diseases can be studied through linkage analysis, DNA makers, and genome sequencing.

3. Pedigree Analysis and Patterns of Inheritance

The pedigree analysis technique is used to study the inheritance patterns of genetic diseases by examining family trees and medical histories. Pedigree diagrams visualize the relationships within families to understand the contribution of genetic factors to various diseases. During the late 19th and early 20th centuries, the practice of pedigree studies can be traced back [10].

One of the earliest pedigree analyses is the inheritance of haemophilia, a bleeding disorder prevalent in Europe. The steps involved in pedigree analysis are collecting detailed family information, constructing a pedigree, analyzing the pedigree, interpreting the results, and follow-up testing.

Inheritance is the natural process by which genetic diseases are passed from parent to offspring. The five primary modes of inheritance are autosomal dominant (inheritance probability is 1:2), autosomal recessive (inheritance probability is 1:4), X-linked dominant (negligibly low for males, 100% for females), X-linked recessive (inheritance probability is 1:2 for males or 1:4 for all offspring) and Y-linked inheritance (only in males). Another rare form of inheritance is mitochondrial inheritance, which is a matrilineal inheritance [10]. Not all genetic conditions will follow these patterns. The patterns of inheritance are not easy to define for complex diseases. The chances of developing a complex genetic disease depends on several factors, namely, the number of relatives affected, how closely one is related to the affected individual(s), similarity of the shared environment and lifestyle factors; age, sex, ethnicity, age of onset, and disease severity in the affected relative. Pedigree analysis has its limitations and challenges. These include incomplete information, complex inheritance patterns, small sample sizes, non-paternity or non-maternity, environmental factors, and ethical considerations [10].

Pedigree studies have now become an even more powerful technique for understanding the inheritance patterns of genetic diseases with the advent of DNA markers.

4. Cytogenetic Analysis

During the metaphase of the cell cycle, cytogenetic analysis examines the banded pattern of all chromosomes. Cytogenetic analysis involves cell culture from the source, harvesting of cells, chromosome preparation, banding, microscopic analysis, and the production of karyotypes. Clinicians use cytogenetic studies mainly to investigate a family history, abnormal ultrasound, biochemistry findings, advanced maternal age of >35 years, recurrent miscarriages, abnormal non-invasive prenatal test results and multiple non-syndromic congenital anomalies [11]. Common cytogenetic studies include karyotyping, fluorescence in-situ hybridization, spectral karyotyping, and chromosomal microarray analysis.

4.1 Karyotyping

Karyotyping is the process of ordering and pairing of chromosomes to detect chromosomal abnormalities. Conventional banded karyotyping is the gold standard for diagnosing, classifying, assigning prognosis, and managing complex diseases [12]. Banding patterns can be achieved in different forms, such as Giemsa-banding, Centromere-banding, Quinacrine-banding, and Reverse-banding. Karyotyping allows for studying structural anomalies, such as deletions, duplications, insertions, inversions, and translocations, as well as numerical abnormalities such as trisomies of chromosome 13, 18, or 21, and monosomy, triploidy, or tetraploidy of chromosomes. Cytogenetic testing can be performed prenatally and postnatally.

4.2 Fluorescence in-situ Hybridization (FISH) and Spectral karyotyping (SKY)

Integration of molecular techniques with classic cytogenetic analysis gave rise to molecular cytogenetics. Two essential diagnostic techniques in molecular cytogenetics are FISH and SKY. FISH detects chromosome abnormalities targeting specific DNA sequences using fluorescently labelled probes that attach to complementary DNA. FISH testing involves determining the presence, absence, position, and copy number of DNA segments with the help of fluorescence microscopy. FISH can be performed both in the interphase and metaphase of the cell cycle. FISH can detect the microdeletion or microduplication of genes to assist in diagnosis, prognosis, and therapeutic management of several genetic diseases [13]. SKY, a relatively novel technique, is used to identify all human chromosomes, each labelled with different fluorochromes. This allows us to visualize all the chromosome pairs simultaneously to detect complex rearrangements and translocation within and between chromosomes [14].

4.3 Chromosomal Microarray analysis (CMA)

CMA is used to screen thousands of individual DNA sequences and provide precise information about the location(s) of any identified aberrations in a single experimental run. CMA helps to diagnose subjects lacking an apparent syndromic phenotype and allows the detection of clinically significant microdeletions or duplications. Microarray-based comparative genomic hybridization (aCGH) and single nucleotide polymorphism (SNP) arrays are subtypes of CMA. Like FISH, oligonucleotide probes attached to fluorescent dyes are used to label genomic DNA through hybridization. This helps to detect genomic copy number changes or minor genetic imbalances, such as gain or loss of chromosomal material [15]. Since the whole genome sequencing of several mammals is complete, a crucial next step involves using microarrays to catalogue all transcription units and identify their expression patterns in healthy and diseased individuals.

5. Next-generation Sequencing (NGS)

NGS provides susceptible and accurate high-throughput platforms for large-scale genomic testing. The workflow of NGS technologies is presented in Figure 1. In NGS, multiple genes can be tested in case-control or family-based studies, in parallel across numerous samples, saving time and money over performing multiple individual assays. Therefore, NGS has proved to be a compelling approach for investigating complex diseases quickly and efficiently as a single genetic test to identify and reliably characterize the comprehensive spectrum of genomic variations [16].

5.1 Whole Genome Sequencing (WGS)

WGS identifies all the genes, their variants and pathways that may have subtle phenotypes that are difficult to study biochemically. WGS also helps to understand the genomes' noncoding regions, introns, promoters, and telomers [17]. WGS provides the primary coverage of the entire human genome in regions not covered by other methods but even within regions targeted by other methods [18].

The Human Pangenome Reference Consortium [19] of the National Human Genome Research Institute presents a first draft of the human pangenome reference (GRCh38) assemblies, which have analyzed the genomes of diverse populations to represent the genomic landscape. It identifies about 90 Mb of additional bases derived from structural variations and reduces error to 1 base error per 200,000 assembled bases [19].

The workflow of WGS is given in Figure 1 (a). The essential applications of WGS include: (1) screening of newborn and pediatric diseases, (2) drug trials and pharmacogenomics, (3) regulatory variation and expression of quantitative trait loci (eQTLs), (4) investigation of rare tumor types, (5) family disease pedigrees and (6) large cohorts with extensive phenotyping. Shotgun sequencing is a classic strategy for whole genome sequencing.

5.2 Epigenome Analysis

Epigenomics includes understanding higher-order chromatin folding and covalent modifications of histone tails, attachment to the nuclear matrix, packaging of DNA around nucleosomes, DNA methylation and noncoding RNAs. NGS-based methods for epigenetic analysis include methyl-seq, ChIP-seq, and ATAC-seq. Integration of this massive amount of data promises to revolutionize our understanding of gene-environment interactions and offers unique ways to diagnose and treat complex human diseases [20]. The workflow for epigenome analysis is given in Figure 1 (b).

5.3. Whole Exome Sequencing (WES)

WES is a technique for sequencing all the protein-coding regions of genes in a genome. About 85% of disease-causing mutations lie in the exome [21]. WES is a powerful and reliable tool to identify population-specific, low and rare frequencies of all genetic variations associated with complex disease [22]. The main categories of exome capture technology are solution-based and array-based. In gene- and protein-interaction studies and pathway analyses, WES aids in discerning the genomic variations and reducing the noise generated by voluminous benign variations in complex diseases. The essential applications of WES are rare variant mapping in complex diseases, discovering Mendelian disorders, and clinical diagnostics. The workflow for whole Exome sequencing is given in Figure 1 (c).

5.4 Clinical Exome Sequencing (CES)

CES is a test for identifying disease-causing genomic variants that code for specific proteins. CES is a subset of WES as it covers a limited number of genes. CES is a rapid and common molecular diagnostic technique for those suffering from rare, mendelian, and complex diseases [23]. Examples include Cystic fibrosis, Haemophilia, and Breast cancer. The workflow for CES is given in Figure 1 (d).

5.5. Targeted Gene Sequencing (TGS)

TGS is a sensitive, rapid, more cost-effective, and robust method that delivers accurate, easy-to-interpret results in a single assay for identifying common and rare genomic variants. Examples: KRAS, TP53, BRAF, and EGFR are targeted across various cancer types [24]. It focuses on a panel of genes or targets known to have strong associations with disease pathogenesis and clinical relevance, offering greater sequencing depth and reducing data burden. The workflow for TGS is given in Figure 1 (e).

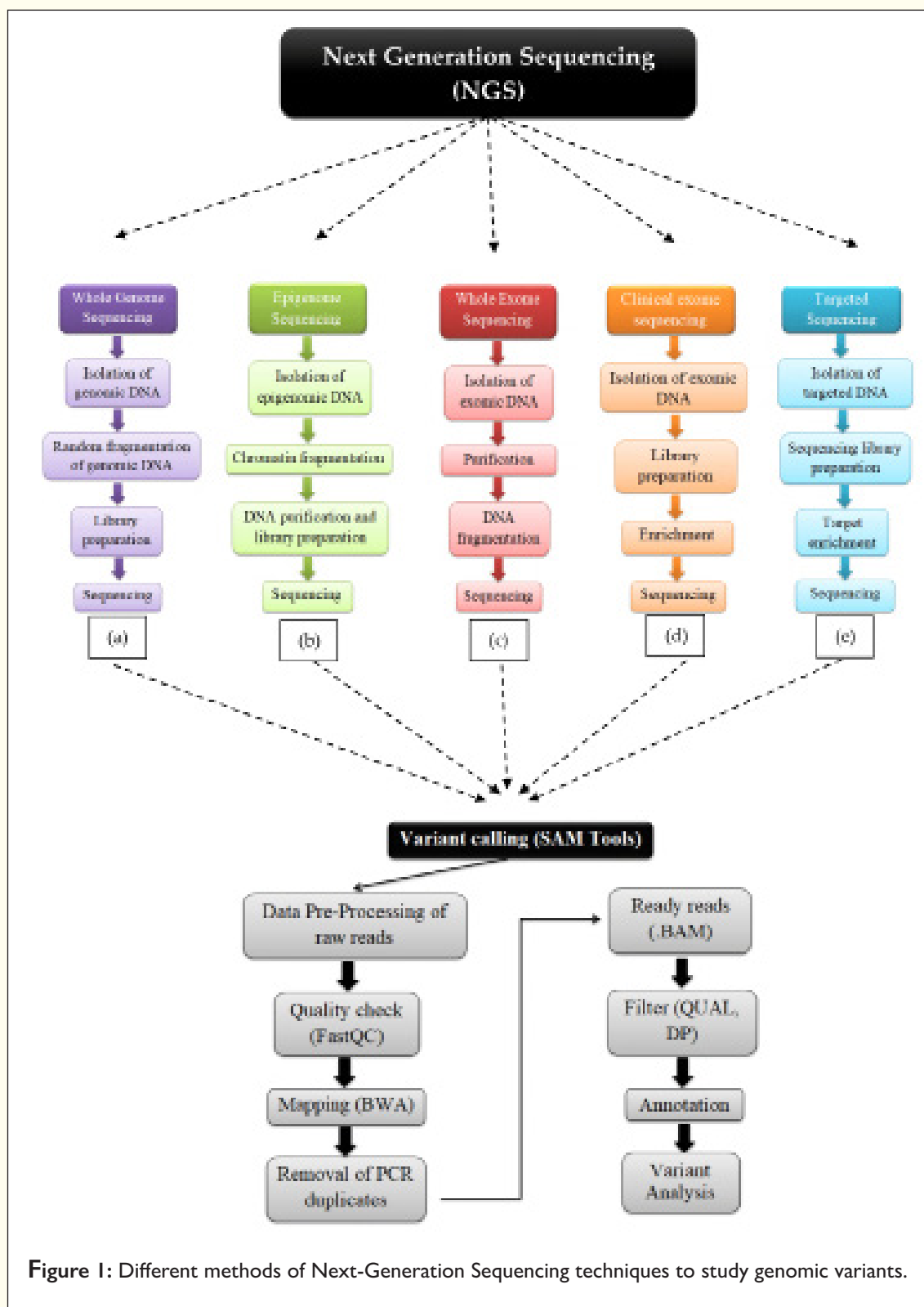
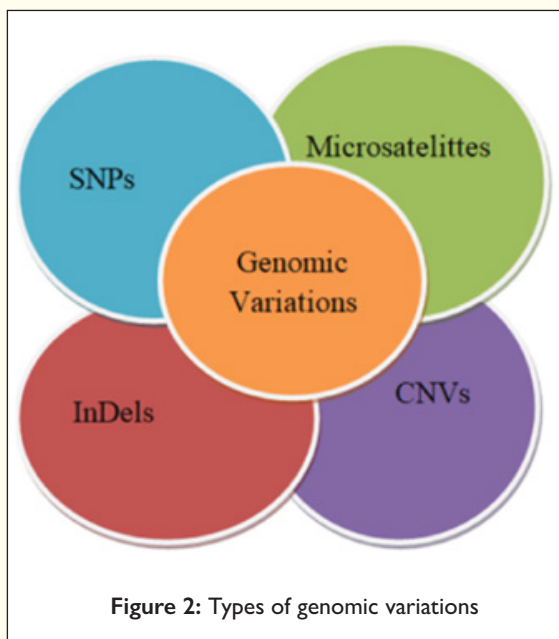


Figure I: Different methods of Next-Generation Sequencing techniques to study genomic variants.

6. Analysis of Genomic Variations



Genomics is a dynamic field in biology that revolutionizes the diagnosis and prognosis of diseases like pathology, radiology, or biochemistry. Although 99.6% of genome sequences are identical in all humans, the 0.4% differences amount to millions of genomic variations in the human population [25]. The genomic variations, namely, single nucleotide polymorphisms (SNPs), Microsatellites, Insertion/deletion (InDels) and Copy number variations (CNVs), are the most powerful tools for the analysis of disease genomes [26, 27] (Figure. 2).

The pathogenicity of identified missense variations can be validated with various prediction tools. Sequence conservation profiling, protein stability changes, homozygosity mapping, and regulatory functional SNPs can be predicted, and different statistical analyses can be employed to analyse the significance of results. NGS allows the detection of common ($MAF > 0.05$), uncommon ($MAF < 0.05 - > 0.01$), and rare ($MAF < 0.01$) genomic variations and de novo variants involved in complex and mendelian diseases, thereby facilitating the comprehension of the genome architecture and its function [28-30].

6.1 Single Nucleotide Polymorphism (SNP)

SNP is a nucleotide location with a high substitution rate in individual samples from a population [31]. SNPs are present in about 3% of the coding and noncoding DNA in the genomes. About 10 to 30 million SNPs are identified in the human population. SNPs are highly polymorphic and serve as biological markers to understand population structure and genetic diversity, allowing us to build high-density genetic maps associated with disease [32]. Using DNA microarrays, millions of SNPs can be examined at the same time more effectively [33]. Many diseases are diagnosed with the association of SNPs and verified in the dbSNP and genomAD databases.

6.2 Microsatellites

Microsatellites are tandem repetitive DNA segments of 1 to 6 base pairs scattered throughout the genome. These are inherited in Mendelian inheritance patterns, highly polymorphic and diverse, and act as prominent genetic markers [34]. Microsatellite repeat expansions manifest in several diseases.

6.3 Insertions and Deletions (InDels)

InDels are the short segments of DNA with the size of 100 to 1000 base pairs that have been inserted or deleted from the genome [26]. InDels results in frameshift and non-frameshift variations. These are highly associated with many complex diseases [35] including neurodegenerative conditions like Alzheimer's disease or physical conditions like Cystic Fibrosis.

6.4 Copy Number Variations (CNVs)

CNVs are deletion or addition of 1 kb up to several Mb segments of the genomes with $>90\%$ identity between the genomes of different individuals. CNVs are present in the population with fixed starting and ending positions. These account for a large portion of human variability [36], tremendously impacting the screening, diagnosis, prognosis, and monitoring of several diseases [37]. CNVs are classified into two main categories, based on sequence length. The first includes copy number polymorphisms (CNP) – highly prevalent in the general population, with an overall frequency of 1% or more and typically associated with genes that encode proteins for drug detoxification and immunity. The second category of CNVs include variants ranging in size from hundreds of thousands to over 1 million base pairs. These rare variants are observed disproportionately in patients with mental retardation, developmental delay, schizophrenia, and autism.

7. Drug Discovery for Genomic Variants

The enormous human individual sequenced data and genomic variations have expanded the range of therapeutic targets in drug design and drug discovery. NMR spectroscopy, protein purification, and high-throughput crystallography have also made the structural details of protein–ligand and protein complexes available [38, 39]. These techniques lead to molecular docking or computeraided drug design (CADD), which uses the techniques of computational chemistry, molecular modeling, molecular design and rational drug design to design drugs for therapeutics, using ligandbased and structure-based methods [40].

Molecular target-based drug discovery has become the key to identifying potential druggable targets [41, 42]. NGS provides genes, their variants and how they affect the protein structure. A protein target associated with disease pathophysiology is identified using direct biochemical approaches, genetic interactions, and computational inference methods [43].

A chemical library of small molecules is essential in the drug discovery process. The number and diversity of commercially accessible chemical compound libraries are available for the pharmaceutical industry and academic investigators. Small drug molecules account for ~80-90% of marketed treatments and offer several benefits, including well-defined structures, relatively simple manufacturing, oral administration, and primarily non-immunogenic characteristics. These drug molecules can also cross the blood-brain barrier and reach the central nervous system.

CADD is typically used in three ways in the drug discovery process: (1) to reduce large compound libraries into smaller sets of predicted active compounds, (2) to guide the optimization of lead compounds, and (3) to design novel compounds. The drug screening results are entered into a database and examined with bioinformatics software. For single-concentration screening, primary screening hits are chosen based on criteria such as inhibition >50%, IC₅₀ <5 M and efficacy >70% [44]. The principal hits consider real chemicals and delete false positives and non-specific chemicals.

8. Personalized Genomic Medicine (PGM)

PGM uses information and data from a patient's genotype and phenotype to stratify disease, select a medication, provide therapy, and initiate preventative measures suited to that patient at the time of administration. This is a new, comprehensive, and integrated approach to disease management and wellness. Most drugs are not effective or partially effective in 60% of the treated patients. Side effects are responsible for millions of deaths and hospitalizations. Predictive toxicology for new drug candidates can predict which individuals will benefit, and those who might be at greater risk for experiencing severe side effects can be identified [45].

The number of targeted treatments in the pipeline for all diseases is increasing dramatically. For instance, the actress Angelina Jolie made headlines with a proactive double mastectomy after tests revealed she carried BRCA1, the same mutations for breast cancer as her mother, who died from the disease. Genes are not destiny, but they indicate suitable decisions about our health and healthcare. As in Jolie's case, this can change our future [46, 47]. Potential benefits of PGM are to predict disease susceptibility, customize disease-prevention strategies, improve disease detection, preempt disease progression, shift the emphasis in medicine from reaction to prevention, prescribe more effective drugs, and avoid prescribing drugs with predictable side effects. PGM helps to reach the point where all medicines are linked to diagnostics [48]. PGM is a promising treatment for improved human welfare.

9. Artificial Intelligence (AI)

AI is the computational simulation of human intelligence. In clinical diagnostics, AI is described as any computer system that can accurately analyze health data, particularly in its original state as viewed by humans. AI can analyze enormous amounts of clinical diagnostic data and genome variation data in various therapeutic situations and contribute to the efficient interpretation of massive and complicated datasets [49, 50].

First, numerous algorithms have been created employing various AI models to discover high-quality genomic variations sensitively and precisely associated with disease. AI also helps to identify long noncoding RNAs, generate protein-coding DNA sequences, and design DNA probes for protein-binding microarrays. Deep learning is the best way to analyze these data sources and complete genomic modelling tasks as the genomic data sets grows exponentially.

Second, AI assists in designing and screening drug molecules and analyzing clinical trials. At the gene level, AI can help to predict the binding affinities of transcription factors, DNA- and RNA-binding proteins, cisregulatory/enhancer elements, DNA methylation sites, histone modifications, chromatin accessibility, transcription start sites, tissue-regulated splicing, gene expression and translation efficacies, transcriptome patterns, microRNA precursors and binding targets, variant calling, noncoding and coding variants pathogenicity [51]. Therefore, AI is one of the strategies to address all kinds of clinical and genomic issues to prevent, treat, and manage diseases by potential drug molecules.

10. Discussion and Conclusion

Although efficient technologies are available, we have several limitations to treating and preventing genetic diseases. Some limitations are the need for more public awareness, current knowledge of the technology, cost of the diagnosis, and proper diagnostic skills. Special training on recent technologies must be updated for concerned persons, including the medical community and researchers.

Some of the recommendations for the implementations include: (1) Diagnostic chips from the identified disease-specific, population-specific variants can be established; (2) Effective integration of genomic, pathological, and clinical data for effortless translation of research data can be enhanced; and (3) These multimodal approaches will effectively assess the effect of variations on protein function through different perspectives and present an opportunity to develop unique biomarker panels for identifying pre-symptomatic individuals with complex diseases.

Finally, understanding the causes and consequences of genetic mechanisms provides meaningful insights into disease genesis and progression. With systematic improvements in the latest software support, NGS data analysis has become an accessible reality to researchers and clinicians. This has paved the way for improved knowledge of the complex interplay of genes and their mechanisms of action in complex human diseases, together with the development of novel treatment and management strategies. Thus, identifying high-risk causal genes and their variants enables research groups to further the discovery process, leading to personalized, targeted therapeutic interventions.

Author Contributions: Conceptualization, Nallur B.Ramachandra; methodology, Chavadapur S. Srushti.; Kommerahalli R. Meghana.; resources, Chavadapur S. Srushti.; Kommerahalli R. Meghana.; data curation, Chavadapur S. Srushti.; Kommerahalli R. Meghana.; writing—original draft preparation, Chavadapur S. Srushti.; Nallur.B.Ramachandra.; writing—review and editing, Chavadapur S. Srushti.; Kommerahalli R. Meghana.; Nallur.B.Ramachandra; supervision, Nallur.B.Ramachandra.; funding acquisition, Department of Atomic Energy (DAE), Government of India, Mumbai Raja Ramanna Chair (RRC) scheme.; Indian Council of Medical Research- Senior Research Fellowship (ICMR-SRF), New Delhi. All authors have read and agreed to the published version of the manuscript.

Funding: None

Institutional Review Board Statement: Not Applicable

Informed Consent Statement: Not Applicable

Data Availability Statement: No new data were created or analyzed during this study. Data sharing is not applicable to this article.

Acknowledgments: We thank the Department of Studies in Genetics and Genomics, University of Mysore; DAE-RRC; and ICMR-SRF.

Conflicts of Interest: There are no conflicts of interest. The funders had no role in the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

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Article

Vaginal Sacrocolpopexy in Vault Prolapse: A Case Series

Padmasri R., MBBS.¹, Priyanka Holla, MBBS.², Keerthi A. V., MBBS³

¹Professor & Head, ²Assistant Professor, ³Assistant Professor, Department of Obstetrics & Gynecology, Sri Madhusudan Sai Institute of Medical Sciences & Research, Muddenahalli, Chikkaballapura.

Abstract: Background: Hysterectomy is one of commonest procedures performed in Gynecology. Up to 10% of these patients can present with post hysterectomy vault prolapse. We explore the efficacy of vaginal Sacrocolpopexy in the treatment of this condition. Methods: In a prospective observational study over a period of 7 months, among patients who underwent vaginal Sacrocolpopexy, we noted their demographic data, parity, Pelvic Organ Prolapse-Quantification (POP-Q) staging, intraoperative, postoperative events, and complications. Follow-up was done at 3 months for all patients and at 6 months for 3 patients. Results: Eight patients were studied, all of them had stage 3 or 4 prolapse, 7 underwent vaginal Sacrocolpopexy and one colpocleisis. During post-operative follow up, one patient complained of dyspareunia, one had painful urination, two patients had lower abdominal pain, and three had low backache. Conclusion: Vaginal Sacrocolpopexy is a safe and effective surgical technique for correction of post-hysterectomy vault prolapse.

Keywords: Vault Prolapse, Sacrocolpopexy, Vaginal Fixation

Corresponding Author: Dr. Priyanka Holla Email: priyanka.holla@smsimsr.org

Citation: Padmasri R, Holla P, Keerthi AV. *Awareness: Newer Horizons in Human Excellence*, 1 (1): 60-67.

Academic Editor: KJS Anand.

Received: 12-14-2023

Revised: 12-23-2023

Accepted: 12-29-2023



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1. Introduction

There is no precise definition of post-hysterectomy vault prolapse (PHVP). The joint report by International Continence Society (ICS)/ International Urogynecological Association (IUGA) on female pelvic floor dysfunction defines it as descent of vaginal vault or cuff scar after hysterectomy. When the structures that support the top of the vagina and uterus are not reattached at the time of the initial procedure prolapse of the vaginal vault after hysterectomy may occur [1]. Weakening of these supports over time, will be an additional factor.

Management of PHVP has been a dilemma for decades. A case series from 1960 previously identified the incidence of PHVP as ranging from 0.2% to 43%.[2] More recently, PHVP has been reported to follow 11.6% of hysterectomies performed for prolapse and 1.8% for other benign diseases [3]. The frequency of PHVP requiring surgical repair was between 6% and 8%, as estimated in an Austrian study [4].

The preferred classification for pelvic organ prolapse and vault prolapse is the ICS Pelvic Organ Prolapse-Quantification (POP-Q) system, which is the most comprehensive and widely used approach. Initially, a preoperative urodynamic evaluation was considered

mandatory for all these patients as the incidence of stress urinary incontinence among them was considered high. The current recommendation states that in continent women doing such studies for women with urinary continence results in unnecessary surgery and is not endorsed [5].

At the time of doing a vaginal hysterectomy, adding a McCall's culdoplasty seems to be effective in preventing a PHVP in comparison to a vaginal Moschowitz repair or a simple peritoneal closure [6]. Attaching the uterosacral ligaments to the vaginal cuff in both abdominal and vaginal hysterectomies reduces the incidence of vault prolapse [7].

If, at the end of anterior vaginal wall closure, the vault is at the level of the introitus, a prophylactic sacrospinous fixation should be considered. Whether conservative management is effective for a vault prolapse is not clear as most studies have been done in pelvic organ prolapse. However, pelvic floor muscle training was found to be useful in women with grade I and II Pelvic Organ Prolapse (POP) and vault prolapse [8].

The question of whether subtotal hysterectomy can reduce the risk of vault prolapse has not been settled irrefutably. On the contrary, it results in increased incidence of urinary incontinence and prolapse than does total hysterectomy [9]. The decision for a surgical management is dependent on the symptoms and their effects on the quality of life and daily activities, as well as fitness of the woman for surgery.

Sacrocolpopexy is equally effective when performed either through the abdominal route or the vaginal route. Abdominal Sacrocolpopexy has a lower recurrence rate, less dyspareunia and urinary symptoms like incontinence, but it entails a longer, more invasive operative procedure and a slower recovery rate. Vaginal Sacrocolpopexy takes a shorter time to operate, allows quicker recovery, and is less expensive [10]. Laparoscopic Sacrocolpopexy has comparative efficacy to abdominal sacrocolpopexy with lesser intraoperative blood loss [11]. Robotic-assisted sacrocolpopexy is more expensive, available in fewer centers, and requires a longer duration of surgery due to the learning curve [12].

High uterosacral ligament suspension, where the vaginal cuff is suspended at the level of ischial spines has a higher complication rate such as ureteric injury of 10.9%, bowel and bladder injury, and is usually not recommended [13]. Colpocleisis or closure of the vagina can be considered in frail women, those not fit for prolonged surgery, and those not sexually active [14].

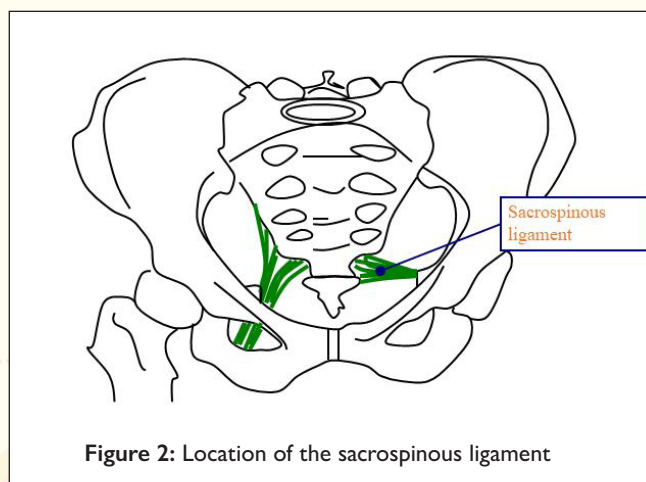
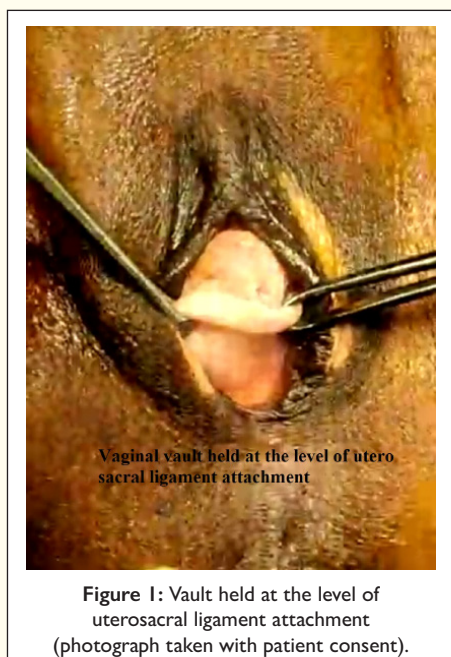
2. Materials and Methods

This prospective observational study was conducted at Sri Madhusudan Sai Institute of Medical Sciences and Research from September 2022 to March 2023. All the patients who presented to the Gynecology department with PHVP were included in this study. After obtaining written informed consent from each patient, history and physical examination, demographic data, parity, previous surgeries, comorbidities, urinary and defecation dysfunctions were noted. Preoperative evaluations included blood counts, routine urine analysis, viral infection screening, renal function, thyroid function, ECG, Chest X-Ray, pelvic ultrasound were performed. Unilateral vaginal sacrospinous ligament suspension was done for all patients except for one patient who underwent colpocleisis. Operative and postoperative complications were recorded

Operative Technique

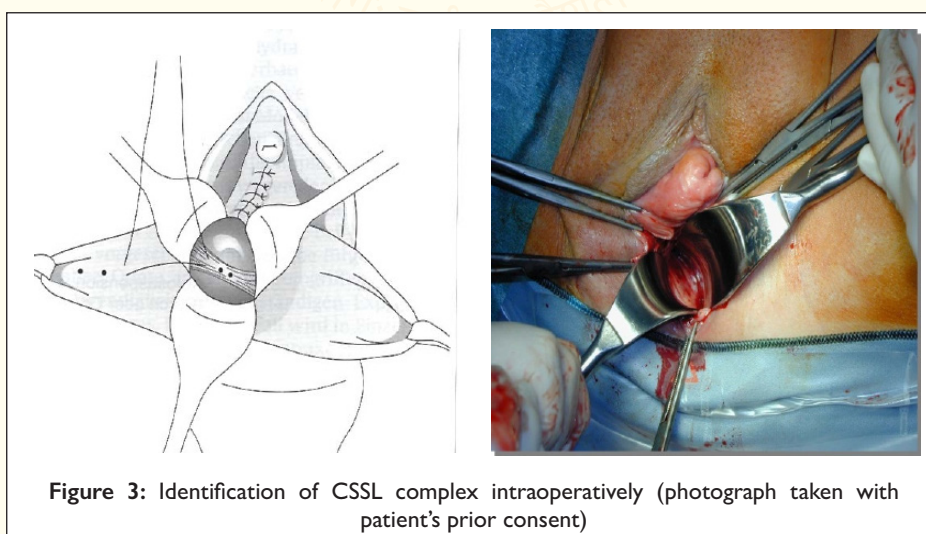
Patients were operated in a lithotomy position under spinal anesthesia. Vault was identified and marked with two Allis forceps, Fig 1. A longitudinal incision was given on the posterior vaginal wall to expose the rectovaginal space, on the right side of the patient, the epithelium was dissected laterally and the pararectal space was opened. After enterocele correction (if indicated), a window was created between the rectovaginal space and ischial spine by blunt finger dissection. Dissection was continued until the ischial spine was reached. Using the ischial spine as a landmark, the sacrospinous ligament was palpated, Fig 2. Then using 3 retractors peritoneum and the rectum were retracted and the sacrospinous ligament was identified, Fig 3. A delayed absorbable suture and non-absorbable suture was used for this procedure. The non-absorbable suture was placed with the help of a long 12 inches needle holder, through the sacrospinous ligament coccygeus muscle complex starting from superior border in an upside-down direction. It was taken 2 cm medial to the ischial spine, to avoid injury to the neurovascular bundle. A second stitch was taken 1 cm medial to the first stitch with delayed absorbable suture. Non-absorbable suture was passed through the vaginal vault full thickness except epithelium

and then tied by half hitch; the other end of the suture was then passed through entire thickness of vagina lateral to the first stitch, creating a pulley stitch. Absorbable suture's ends were passed through vaginal wall full thickness on both sides.



Anterior colporrhaphy was performed, the upper vagina was closed, and lastly, the pulley stitch followed by reinforcing delayed absorbable stitch was tied. This was followed by perineorrhaphy, where required. Tying of sutures brought the sacrospinous ligament in direct contact with the vaginal epithelium and was pulled up.

When healing occurs, the vaginal epithelium is fused with the sacrospinous ligament and the vault remains suspended up. Postoperatively women were given broad-spectrum antibiotics for 5 days. Patients were followed up at 3 and 6 months, postoperatively. Data regarding quality of life, recurrence, complications, functional outcomes, urinary disturbances, bowel disturbances and sexual dysfunction were collected.



3. Results

During the study period of 7 months, a total of 8 patients were included. Mean age of the study group was 57.6 years, with a median parity of 2 children.

Table 1: Patient Characteristics

Characteristics	Value	
Demographic variables	Mean (SD)	Median (IQR)
Age (years)	57.6 (11.7)	56 (52.3-63.8)
Weight (kg)	51.2 (4.9)	50.3 (48.5-52.6)
Height (cm)	151.4 (7.4)	153.5 (149.3-156.5)
BMI (kg/m ²)	22.4 (2.1)	22.9 (20.9-23.8)
Number of children	2.4 (1.3)	2 (2-3.25)
Reproductive history		
Previous abdominal hysterectomy	7	
Previous vaginal hysterectomy	2	
POP-Q: Grade 4 prolapse	5	
Grade 3 prolapse	3	
Cystocele: Grade 2	2	
Grade 3	2	
Grade 4	3	
Rectocele: Grade 1	5	

Among the 8 parous women, 7 delivered at home with help of untrained dais and one delivered in a hospital. Of the 8 studied cases, 5 had prior vaginal hysterectomy and 2 had prior abdominal hysterectomy. Additional surgeries performed on these patients included anterior repair in 6 patients and posterior repair in 5 patients.

None of the patients had peri-operative or early postoperative complications like pyrexia, urinary tract infections, or hematuria. During the follow-up period at 3 months and 6 months, the following symptoms were observed:

Table 2: Post-operative Outcomes

Symptoms	Number of patients
Lower abdominal pain	2
Low back ache	3
Difficulty/ pain in urination	1
Dyspareunia	1

No patients endorsed symptoms of pelvic pressure/bulge, difficulty or pain in bowel movements, urinary or bowel incontinence.

4. Discussion

The true incidence of vaginal vault prolapse after hysterectomy remains unknown. Long-term follow up of these patients would be required with not just a symptomatic questionnaire but also a clinical examination to look for compartment defects. In one 13-year study done on 2,670 patients the incidence of vault prolapse was found to be 0.4% but on pelvic examination, it was found to be 4.4% in all cases of hysterectomies. Further breakup of these data show that the incidence of vaginal vault prolapse is 11.6% when done for genital prolapse, as opposed to 1.8% when the hysterectomy was done for benign conditions [3].

Pre-operative prolapse of grade 2 or more is a risk factor for later developing vault prolapse. Urinary incontinence surgery, previous history of vaginal deliveries, and sexual activity are additional etiologic factors. Vaginal hysterectomy, however, is not a risk factor when done for conditions without pre-operative prolapse or factors related to pelvic floor weakness [15].

Postmenopausal women with surgically managed pelvic floor disorders are at increased risk of developing vaginal vault prolapse after a vaginal hysterectomy, as was seen in our case series. Six out of the 8 women had undergone a vaginal hysterectomy for genital prolapse and were also postmenopausal at the time of surgery. All the six women had a grade 3 or 4 prolapse. Five of them had home deliveries conducted by untrained traditional birth attendants and the parity of these women was greater than two.

As per a study to look at obstetric risk factors for genital prolapse, symptomatic prolapse increased by 3.3-fold in women who had 4 or more children as compared to those who had one child. Excessive stretching and tearing of the pelvic floor being the other predisposing factors while abdominal deliveries were protective [16].

Pelvic floor muscle dysfunction along with anal lacerations have been associated with pelvic organ prolapse. Body mass index, heavy occupational work, and low socioeconomic status are the other risk factors [8]. The women from our study were from a poor socioeconomic background, with poor nutrition, quicker return to heavy work after delivery, and poor spacing between pregnancies.

The incidence of women undergoing surgery for pelvic organ prolapse will rise, as epidemiological data suggests that women aged over 65 years will nearly double. Uterine prolapse is the main contributor to reproductive health problem that influences the women's quality of life. The incidence of uterine prolapse is 7.6% in North India, approximately 20% in East India, and 3.4% in southern India i.e. Karnataka. The World Health Organization reports the prevalence of uterine prolapse to ranges from 2% to 20% in women younger than 45 years of age. 33% of the global disease burden in women is due to reproductive ill health [17].

Surgical techniques for advanced pelvic organ prolapse need to be individualized based on the defects in the various compartments. Suspension of the uterosacral ligaments at the time of hysterectomy has similar anatomic and subjective outcomes to sacrospinous ligament fixation at the end of 1 year and must be considered in all cases of advanced prolapse.

Though abdominal approaches may have increased long-term durability, when counselling their patients, surgeons should consider longer operating times and increased pain and the added cost of these procedures compared to vaginal surgery.

Vaginal vault prolapses occurring post-hysterectomy has several surgical modes of management as discussed above. There are no guidelines to date. Sacrocolpopexy is probably the most commonly performed surgery. The routes vary between abdominal and transvaginal, open, laparoscopic and robotic. Differences in repair may be with and without mesh, or with native tissue. Vaginal sacrocolpopexy was shown to carry a success rate of over 90% and was the most commonly performed surgery followed by abdominal sacrocolpopexy. It could also be combined with or without continence surgery depending on the symptoms. Each procedure has its own advantages and disadvantages.

In our case series, we performed unilateral vaginal sacrocolpopexy in seven women and colpocleisis in one. Sacrospinous ligament fixation (SSLF) entails the placement of sutures to the sacrospinous ligament, which is then attached to the vaginal vault. Its main advantages include shorter duration of surgery, shorter recovery time, and the avoidance of abdominal incisions.

Vaginal sacrocolpopexy is a simpler approach. The technique provides maintenance of sexual function and achieves adequate vaginal length and width. It can also be combined with other reconstructive procedures and additional anti-incontinence surgery [18]. It carries lesser anesthesia risk as it is done under regional anesthesia. The complication rate is low, with blood loss from injury to pudendal/inferior gluteal vessels, requiring transfusion in 4.3% patients. The other complications include nerve damage to the sciatic or pudendal nerves, dyspareunia, and injury to the rectum. Buttock pain is reported in 10–15% of patients, but usually resolves within 6 weeks. The fear of these injuries has resulted in more surgeons opting for abdominal route [19].

Abdominal sacrocolpopexy was associated with a longer operating time, longer time for recovery, and was more expensive than the vaginal approach. The trend towards a lower reoperation rate in the abdominal route compared to vaginal route is not statistically significant [18]. Laparoscopic sacrocolpopexy provides a good anatomical correction but the risk of general anesthesia; mesh erosion, and increased cost are significant disadvantages. By utilizing the vaginal pathway, this approach minimizes incisions and the likelihood of scarring [22].

The prevalence of pelvic floor dysfunction six years after primary surgery was quite high after primary POP surgery in a Swedish study. The incidence of urinary incontinence of 1 or more episodes per week was 41%, feeling of vaginal bulging 18%, and solid stool incontinence was 15%. Only 39% women were sexually active, of which 42% experienced dyspareunia, and 15% refrained from sexual activity due to discomfort or pain [20].

The primary aims of surgical treatment are the restoration of normal vaginal anatomy as well as improvement in vaginal bulge symptoms and the restoration/maintenance of normal bladder, bowel and sexual function. However, most of the studies use only the anatomical outcome as the primary outcome, with POP-Q stages I or 0 defined as the anatomical cure. A recent qualitative study based on patient interviews showed that women are most affected by the actual physical symptoms of prolapse (bulge, pain, and bowel problems) as well as by the impact that prolapse has on their sexual function. Failure of surgery is defined as the vaginal apex descending below the upper third of the vagina, or one of points Ba or Bp being greater than 0 cm, i.e. the anterior (Ba) or posterior (Bp) vaginal wall prolapsing beyond the hymen [21].

Our patients reported that their prolapse symptoms and quality of life were improved at 3 and 6 months after surgery. Unlike previous studies, their prolapse status was also measured by clinical examination before surgery and at 3 months after their operation. None showed a failure of surgery at the end of this study period. None of the patients had pelvic pressure symptoms or difficulty in bowel movements or incontinence post-surgery. Three patients had low backache, one patient had dyspareunia, one patient had dysuria, 2 of them had lower abdominal pain. Statistical significance of post operative complications could not be derived due to small sample size. We will continue to follow-up these patients for a period of 2 years to look at long-term outcomes.

5. Conclusion

Vaginal sacrocolpopexy is a safe and effective surgical technique for correction of PHVP. In the postoperative follow-up of 6 months for a few patients and 3 months for all patients, there was no persistence or recurrence of symptoms. Prophylactic steps during primary surgery can help to further reduce the incidence of vault prolapse.

Author Contributions: Conceptualization: Padmasri R., Keerthi A. V.; methodology: Padmasri R., Priyanka Holla P. N.; writing—original draft preparation: Priyanka Holla P. N.; writing—review and editing: Padmasri R.; visualization: Padmasri R.; supervision: Padmasri R.

Funding: This research received no external funding.

Institutional Review Board Statement: Institutional Ethical Committee Clearance was obtained prior to data collection (Protocol Number: 04/2023).

Informed Consent Statement: Written informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical policy.

Acknowledgments: Dr Kiran Ashok, Urogynaecologist, Dr Chandrashekhar YS, Urogynaecologist, Visiting consultants at Sri Madhusudan Sai Institute of Medical Sciences and Research

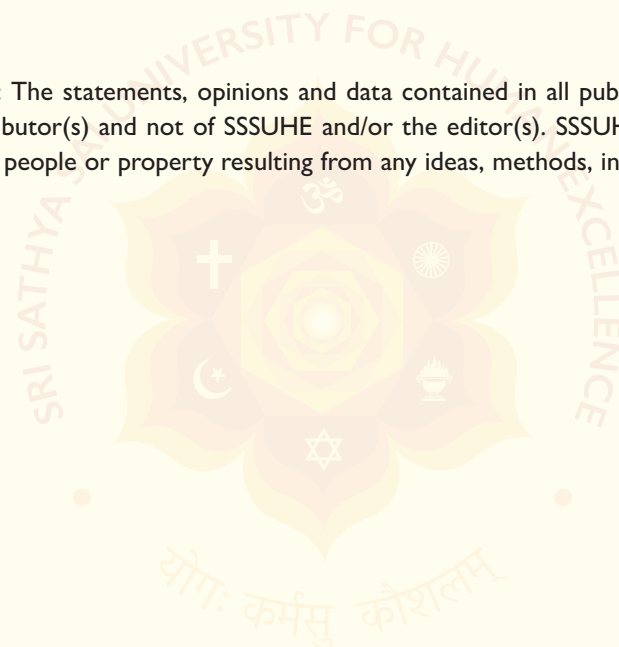
Conflicts of Interest: The authors declare no conflicts of interest.

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Article

Definitions of Resilience in Childhood and Adolescence

Ashley M. Lee¹, Cynthia R. Rovnaghi¹, Zoie V. Carter¹,
Kanwaljeet J. S. Anand^{1, 2}

¹Child Wellness Lab, Stanford University School of Medicine, Stanford, CA, USA

²Department of Pediatrics, Anesthesiology & Pain Medicine, Stanford University School of Medicine, Stanford, CA, USA

Abstract: Research on resilience has traditionally focused on adults, in relation to their psychosocial and work-related functions. Here, we seek to harmonize the interdisciplinary perspectives of resilience, trace the roots of resilience to infancy and early childhood, move beyond a debate on the binary (state versus trait) characterization of resilience, emphasize resilience over vulnerability across the lifespan, and explore solutions for building resilience in childhood and adolescence. We describe the adaptive and flexible brain synchronization effects of resilience from early childhood to adolescence that shape evolving self-concept clarity and hypothalamic-pituitary-adrenal (HPA) axis regulation. Resilience in the context of age-associated adaptation, thriving, and coping strategies (protective factors) is not merely resistance to adversity. Rather, it may be viewed as prioritization of positive childhood experiences (PCEs) that can alleviate toxic stress, build the neural circuitry supportive of mental stamina, enhance prefrontal control of thoughts, emotions, and actions, and thus, prevent or reduce the childhood health outcomes related to early adversity. A PCEs repertoire is cultivated through the practice of five strengthening orientations: word orientation, religious orientation, belief in family, achievement orientation, and adaptability of family roles. In the absence of PCEs, threat detection, reward-related, and cognitive control processes are linked behaviorally to heightened emotional reactivity, blunted reward responsivity, poor emotion regulation, delayed discounting, and risk-taking behaviors. Resilience is a metric to gauge an individual's reaction to and recovery from daily acute stressors and cumulative chronic adverse conditions.

Citation: Lee AM, Rovnaghi CR, Carter ZV, Anand KJS. *Awareness: Newer Horizons in Human Excellence*, 1 (1): 68-83.

Academic Editor: SP Setty.

Received: 12-14-2023

Revised: 12-23-2023

Accepted: 12-29-2023

Keywords: resilience; adverse childhood experiences; positive childhood experiences; neurobiology; biomarkers; adolescence; child development

Corresponding Author: Ashley Lee, ashley22@stanford.edu



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1. Introduction

The word resilience stems from a Latin verb 'resilire', meaning "to leap, to spring back, or spring forward". Initially applied in physics, after it was introduced to human psychology, it was readily adopted by various authors; for example, by Abraham Maslow (1948) to explain 'self-actualization' [1], by Viktor Frankl (1985) in 'Man's search for Meaning' [2], Robert Ewen (2010) in personality theories [3], or Martin Seligman (2011) in 'Flourish' [4]. The concept of resilience, particularly in the context of adverse childhood experiences (ACEs) and early life adversity (ELA), has garnered significant attention across various disciplines. Collectively, many disciplines recognize

the importance of preventing ACEs and mitigating their effects through effective coping strategies, with resilience being an innate ability to recover and prepare oneself for future potential difficulties. Positive childhood experiences (PCEs) are increasingly recognized to offset adversities as measured by changes in behavior, health outcomes, academic performance, or delinquency [5]. Nevertheless, there remains a lack of clarity in the precise role and definition of resilience [6]. This ambiguity is especially prominent in adolescent development, where individual responses to trauma are notably diverse [7, 8].

A central debate in understanding resilience revolves around its characterization as either a state or a trait. When viewed as a state, resilience is seen as a dynamic attribute that can be developed and strengthened in response to adversity. If considered a trait, it is perceived as an innate quality that determines how individuals recover from stress or trauma. This binary framework, while useful, oversimplifies the complex nature of human development. While we acknowledge this controversy and seek to harmonize the definitions of resilience, we also highlight the importance of moving past this debate to prioritize solutions that build resilience.

The discourse on resilience is further complicated by the varied perspectives of different disciplines like psychology, social sciences, pediatrics, and neurobiology. Each contributes valuable insights confined to their areas of study. Current resilience measurement methods primarily focused on recent behaviors may not fully capture the potential for change in resilience over time. Whether the method is a self-reported assessment or functional magnetic resonance imaging (fMRI) scans of the brain, they often rely on the present perception or condition of participants.

Resilience becomes especially important in adolescence, a transitional period where self-concept clarity develops and peer influence outweighs parental guidance. However, without a consistent definition of resilience, it is difficult to investigate its impact on evolving self-concepts, personality, and quality of life.

This review seeks to redefine resilience with a focus on child and adolescent development using a two-pronged approach: first, by synthesizing current methodologies and theories of resilience from various disciplines (Fig. 1); and second, by acknowledging the unique developmental phases of childhood and adolescence as independent variables (Fig. 2). These phases are defined differently depending on their context: in education, they depend on school behaviors or age-related skills, while therapeutic contexts prioritize social interactions or neuro-biological changes. This paper will focus on the neurobiological developments as observed by the brain synchronization between the child and parent, and later transition to child and peer synchronization [9]. We also explore ways to operationalize resilience, tailored to the specific needs and experiences of adolescents and solutions based on parent-child relationships and spirituality.

2. Interdisciplinary Approaches to Define Resilience

2.1. Psychology/Psychiatry

In psychology, resilience is understood as adaptive coping in response to adversity influenced by social learning from parent-child dynamics, teacher-student relationships, and community environments. These interactions are protective factors that foster resilience, including five strengths: word orientation, religious orientation, belief in family, achievement orientation, and adaptability of family roles. Resilience can be measured through constructs such as social competence and emotional regulation [10].

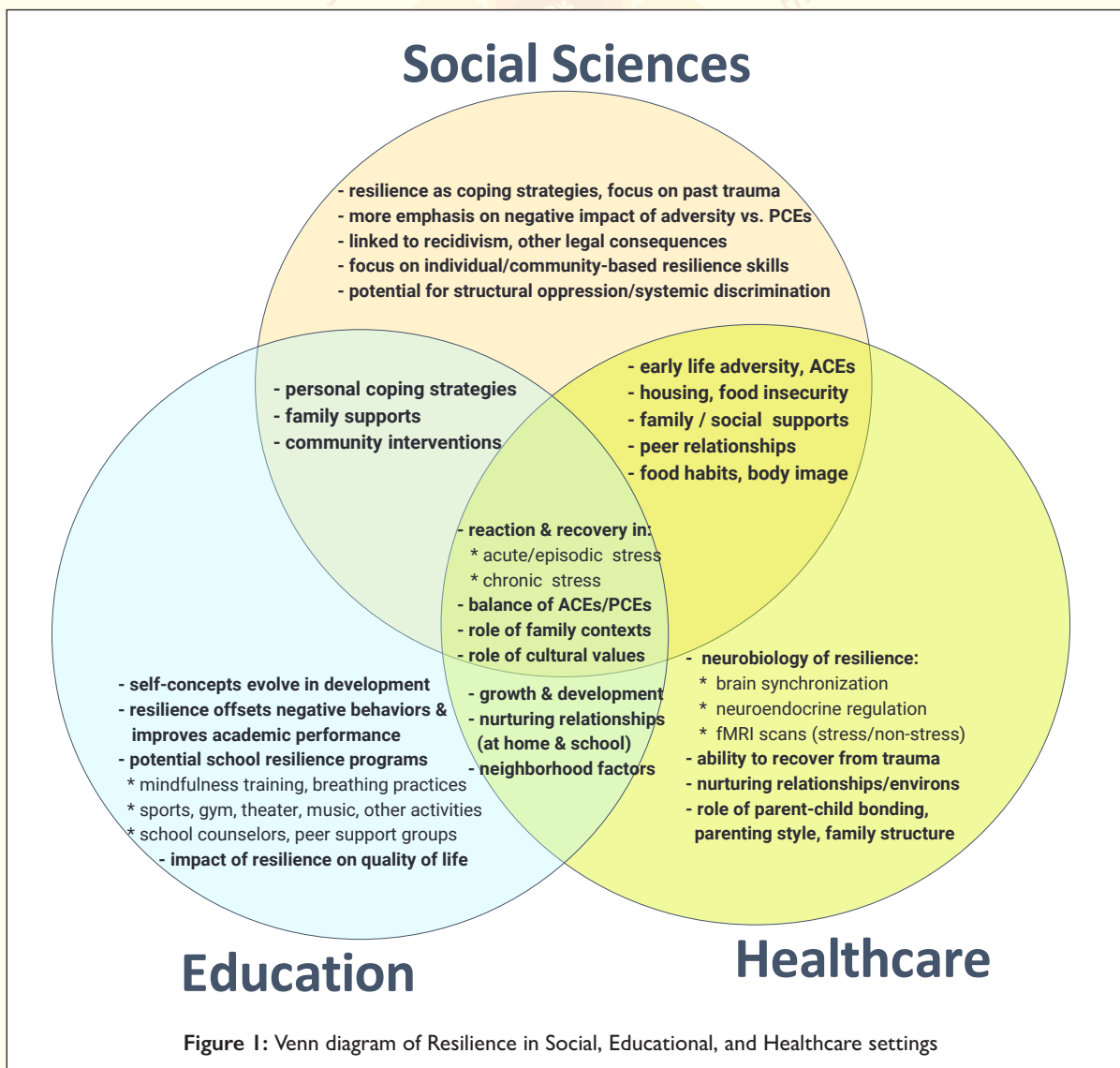
Distinguishing resilience from resistance to adversity, particularly among communities facing structural racism, was challenging because of the overlap between these two constructs. In psychiatry, researchers observed an association between the long-term effects of adversity and structural discrimination on child psychology and subsequent mental health, coupled with maturational changes in the hypothalamic-pituitary-adrenal (HPA) axis [11]. The HPA axis controls cortisol levels and follows a diurnal rhythm with higher morning levels that gradually decrease during the day. Cumulative stressors can lead to HPA-axis dysregulation, showing a “blunted” or “heightened” cortisol awakening response (CAR) [11-13]. During puberty, hormonal changes mediate cortisol stress reactivity, allowing these endocrine changes to become more visible [13]. Salivary samples are often used to observe diurnal cortisol levels, which is a measure of acute stress and therefore susceptible to behavioral state reactivity [11]. However, cumulative stressors are best measured through hair

cortisol concentrations (HCC) that accurately measure chronic stress [14]. Longitudinal trajectories of HCC measured at yearly intervals showed the direct impact of early life stress (ELS) on children. This allostatic load, or cumulative burden of ELS exposures is directly associated with HPA-axis dysregulation [15, 16] and predicts their later susceptibility to mental health disorders [17, 18].

In addition to biological observations on stress and its impact on mental health, other researchers focus on a patient's current emotional state and attitude. Using psychiatric assessments, such as the 14-Item Resilience Scale (RS-14) that evaluates self-reliance, purpose, equanimity, perseverance, and authenticity, where resilience is defined as a stable trait. Although RS-14 suggests resilience as a stable trait, the wording of questions imply potential variability of responses over time, supporting a more dynamic interpretation of resilience. Other measures like the Strengths and Difficulties Questionnaire that observes current behaviors and the Connor-Davidson Resilience Scale that assesses a patient's ability to handle stress [8, 19] are often measured repeatedly to assess resilience as a dynamic state. Most psychological stressors often have psychosocial consequences, prompting the research on resilience in the social sciences.

2.2. Social Sciences

In the social sciences, resilience is the capacity to adapt and thrive in new environments while preserving cultural heritage and past experiences, particularly when integrating into a new society [20]. It includes overcoming challenges associated with marginalization and managing feelings of hostility or alienation that may arise in unfamiliar settings. Social resilience focuses on maintaining one's quality of life, cultural identity, and family values in the face of change and drawing inner strength from these past experiences.



When applied to social work services or the legal system, resilience is often synonymous with coping strategies where “positive resilience,” or “mental stamina,” are viewed as qualities that can counteract negative outcomes in individuals who have faced violence or trauma in the past [21]. This interpretation underscores the potential for resilience to be cultivated or strengthened over time. Resilience is often included in discussions of past trauma but not as a solution, because the negative impacts of trauma are emphasized over the potential for change. Criminal justice studies also compare the number of ACEs and PCEs that justice-involved adolescents have experienced [22] and focus on the accumulation of PCEs rather than a single positive experience [23]. These studies have linked high levels of PCEs to reductions in recidivism and other legal consequences [22-24] (Figure 1).

Social supports are often designed to build resilience [25-28], but resilience assessments are not included as outcomes in social programs. In one meta-analysis of 79 anti-bullying programs, resilience only received a cursory mention to prevent bullying. School programs for elementary to high school students generally targeted individual skills such as emotional regulation, along with community-based skills such as empathy and bystander intervention [29], but did not assess changes in student resilience. Most psychological and social interventions to promote resilience in children and adolescents have significant impacts on their physical and mental health, thus prompting research to define and measure resilience in healthcare settings.

2.3. Pediatrics

In pediatrics, resilience is conceptualized as the ability of children to recover from adverse childhood experiences, occurring at different developmental stages, directly contrasted with vulnerability in a child's social ecology [30]. ACEs adversely impact adolescent and adult health, heightening risks of obesity, depression, substance abuse, among many others [31-40]. Consequently, pediatricians focus on PCEs as protective measures to mitigate the long-term outcomes associated with ACEs [5, 41, 42]. For example, the Healthy Outcomes from Positive Experiences (HOPE) framework primarily focuses on the parent-child relationships since adolescents exposed to nurturing relationships often foster resilience [43, 44]. Factors measured under HOPE, including the housing environment and the mother's health, are associated with the child's resilience [45]. For example, in a state-wide sample, adults who reported higher numbers of PCEs had lower rates of these negative mental health outcomes [46]. Similar trends were observed between school success factors, including attendance or engagement where resilience was associated with the balance of ACEs in comparison to PCEs [45, 47]. Research to understand the underlying mechanisms of resilience vs. vulnerability in children exposed to ACEs or other forms of adversity have primarily used the tools and techniques available in epigenetics and neurobiology.

2.4. Neurobiology

In neurobiology, resilience is centered around identifying structural brain markers, such as gray matter volume in areas associated with executive function and emotion regulation [48, 49]. Resting-state fMRI studies suggest that the amygdala and orbitofrontal cortex are key areas of interest, as they play a significant role in the emotional processing associated with resilience [50]. Exposures to ELS accelerate the frontoamygdala development, which regulates socioemotional processing in resilience. Greater ELS severity leads to early emergence of inverse frontoamygdala connectivity, which reflects more mature connectivity and may protect against accelerated biological aging [51].

These changes in neural circuitry, specifically in threat detection, reward-related, and cognitive control processes, are linked behaviorally to heightened emotional reactivity, blunted reward responsivity, poor emotion regulation, and delayed discounting. These promote risk-taking behaviors, such as smoking cigarettes, drinking alcohol, and eating high-fat, high-sugar foods [52]. With heightened neural responses to threats, children have a higher emotional reactivity in threatening environments, but with blunted reward responsivity, they seek out risky high-rewarding stimuli. The frontoparietal executive control network is altered by ELS, and they cannot delay immediate gratification despite its potential consequences. While their fast, reflexive responses were advantageous in adverse environments, these children find it harder to make positive choices with lifelong benefits [52].

Neurophysiology studies have examined concepts such as brain synchronization to investigate child-parent relationships. Behavioral and biological signals during social interactions align with one another in brain synchronization. Technologically assisted communication reduces the inter-brain synchrony, which is often associated with less eye contact and empathic engagement [53]. Remote interactions activated only one significant cross-brain cross-hemisphere link between mother-child pairs, eliminating the robust right-brain-to-right-brain connectivity during social moments that communicate socio-affective signals. Conversely, live interactions created 9 cross-brain links from densely inter-connected frontal and temporal brain areas in mother-child pairs, showing that screen interactions harm brain maturation and development of resilience in infancy [53]. Supportive data for these studies show increased screen time linked to autism [54, 55], language processing delays [56], and other detrimental effects on infant development.

Neuroendocrine studies of resilience focus on oxytocin as the hormone that regulates pro-social behaviors, promotes social interactions, and enhances inter-brain synchrony during social coordination tasks [57]. Due to the pandemic, social media and other online communication methods were especially relied upon; thus, it is particularly important to investigate the impact of these programs on the social interactions of children born during the pandemic [58-60]. It is clear, however, that not all pandemic-born children were affected to the same extent. Pandemic-related effects on social interactions, executive functions, and resilience in early childhood were greatly influenced by parental attitudes, rearing practices, and cultural values in each family [61].

2.5. Cultural Psychology

Resilience is closely tied to self-identification within a community and self-concept clarity, which is a coherent understanding of one's self [62]. Environmental influences, such as neighborhood biases, bullying experiences in school, or affirmation experiences despite marginalization, significantly shape a child's self-image. This, in turn, has a profound impact on their resilience [63, 64].

Cultural psychology offers insight into varying interpretations of resilience across cultures. For example, American culture views resilience as individual strength, while others emphasize the collective attribute, emphasizing family and community support as essential components [65, 66]. Additionally, different cultures may emphasize various coping mechanisms, such as a higher reliance on spirituality among Asians [67]. Like psychiatry, cultural psychology also utilizes various scales and questionnaires to assess factors such as current stressors and coping mechanisms. These tools help to understand resilience in the context of different cultural backgrounds and life experiences.

2.6. Summary of Interdisciplinary Approaches

The interpretations of resilience above highlight four noticeable trends across most fields. First, resilience is increasingly defined as a behavioral state, meaning there is a potential for change over time. Second, the development of resilience or influencing factors begin from birth or early childhood. Third, most measures of resilience do not incorporate the age or developmental stage of the child. Fourth, social programs and community interventions demonstrate that resilience can be learned through observation and active learning through practice. The definition of resilience, gained through self-concept clarity, is the child's innate and/or learned ability to process adversity in the present and to overcome it in the future. In doing so, each child epitomizes the Latin verb 'resilire' – "to leap, to spring forward", to gain mastery and strength from each adverse experience. The following section explores how this happens in early life.

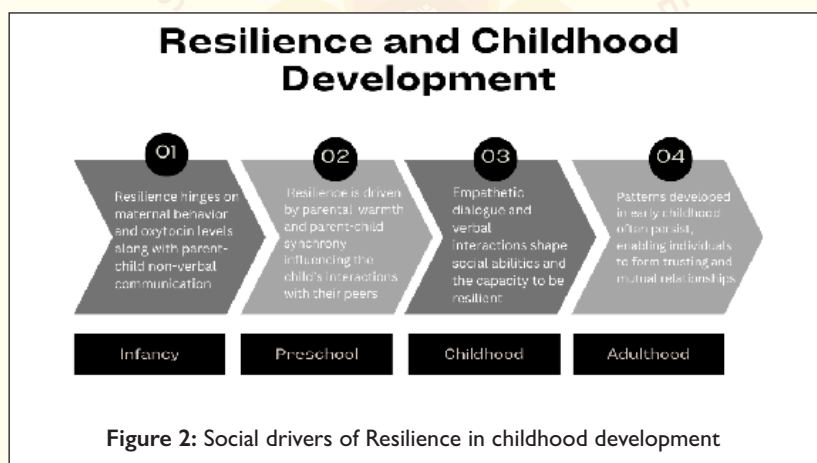
3. Roots of Resilience in Childhood

Through early experiences of infant bonding and brain synchronization between parent and child the modes of developing resilience may change depending on the developmental stage of the child (Figure 2). By studying effects of early caregiving and child temperament on the child's stress and immune systems, Abraham et al. found that greater self-regulation and lower negative emotionality in children were associated with lower baseline levels of secretory Immunoglobulin A (s-IgA, which serves as a critical first line of defense against infections) and salivary cortisol (an acute stress marker) [68]. These relationships were influenced by the quality of early parenting, such that children with low self-regulation had higher s-IgA levels with low parent-infant synchrony, whereas negative emotionality was associated with higher baseline cortisol levels

when parental oxytocin levels were low [68]. This and other studies show that when parental sensitivity and warmth are low, then children manifest higher stress, lower immunity of infection, negative emotionality, and lower resilience. Cortisol regulates the autonomic system to alter physiological responses, and it also contributes to learning from stressful experiences [69, 70]. Salivary (or serum) cortisol levels reflect acute stress [71] but cannot measure cumulative or chronic stress [72-75]. Stress-induced cortisol responses in children are buffered by nurturing parents, at least partially mediated by oxytocin release [75-77]. Multiple lines of evidence suggest that oxytocin inhibits the HPA axis in children and adults [72, 78-81]; it mediates affiliative or bonding behaviors, facilitates parent-infant synchrony, and builds resilience in early childhood [75, 82, 83].

The integrity of subcortical and cortical networks in parents is linked to the child's social outcomes. The development of basic regulatory tactics, more complex self-regulatory strategies, as well as advanced socialization skills in children are impacted by the quality of parenting [84-86]. Similarly, parents' brains also respond (in a coordinated manner) to infant cues. Mothers show higher activations in the amygdala (a region linked to emotional processing), while fathers showed greater activations in social-cognitive circuits. In this study, infant cues were correlated with oxytocin levels for mothers and arginine vasopressin levels for fathers [87, 88].

Thus, recent research highlights the significant role of parent neurobiology and parenting practices in influencing a child's stress-responsive systems, emotions, and social adaptation. This is seen in parent-infant synchrony, which extends beyond mere behaviors, reflecting in their neural activities. The correlations of oxytocin, arginine vasopressin, and cortisol levels between the child and parent already reveal the impact of infant-parent bonding on resilience.



Biobehavioral synchrony includes behavioral coordination, heart rhythm synchrony, oxytocin release coordination, and brain-to-brain synchrony in social cognition. Most previous research relies on a definition of resilience for their study, regardless of the age group; however, a nuanced definition of resilience must recognize a child's developmental stages [30, 89]. In neonates, resilience hinges on maternal behavior and oxytocin levels. Mothers become aware of the neonate's "moments of alertness," the first step to coordination. Infants engage in "rhythmic" non-verbal communication with mothers, influencing their social, emotional, cognitive, and brain development [90]. Toddlers emphasize creative learning through symbolic play and storytelling, while parent oxytocin levels and early synchrony predict the child's synchrony with their best friend or peers. In later childhood and adolescence, empathic dialogue and verbal interactions predominate, shaping social abilities and resilience in the face of adversity. This period marks a shift in attachment focus from parents to peers, crucial for well-being and the social brain's maturation. In adulthood, the familiar rhythms of early childhood persist, enabling individuals to form trusting and mutual relationships [9, 91, 92].

Brain synchronization reflects parent-child bonding, which is significantly disrupted by maternal depression, transmitting emotional regulation and socialization risks can to the child. While having a mental health condition in the family is listed in the ACEs scale, the impact of maternal depression depends on the severity or duration of depression and the child's

age of exposure [93] – the younger the child, the greater and more long-term is its impact on the child's cognitive and behavioral development, socialization and language skills, physical and mental health, and ability to develop resilience [94, 95]. There is no genetic component for depression in their childhood and adolescence, when the child's unmet needs limit the development of their social and cognitive skills then they are at increased risk for anxiety, depression, and low resilience [85, 96, 97]. The cumulative exposures of the child to ACEs, ELA, poor parenting, and social determinants of health, especially during sensitive periods development, are the main drivers of risk in the stress-diathesis model [94]. Children with a history of such exposures clearly need help in academic, social, and therapeutic settings to build, restore, and promote their resilience.

4. Solutions to Promote Resilience

Many approaches to promote resilience have been proposed and are easily available to adults and employees (e.g., www.resilienceresearch.org; www.resilience-leadership.com, www.resilientoption.com; www.ultimateresilience.co.uk; or others), but few if any are specifically designed for children and youth. Here, we discuss two of the approaches that appear to confer the greatest benefit for building resilience in children and adolescents.

4.1. Parental Relationships

Healthcare professionals can play a significant role in normalizing periods of disorganization in infancy by offering support and by recognizing everyday stressors and the “uneven nature of infants’ developmental progress” [98]. With gentle empathetic guidance, parents are better equipped to provide regulatory inputs to their infant, while accurately addressing their child's immediate needs to “repair the child's state.” A consistent failure to understand an infant's needs can have impacts akin to severe neglect [98].

Parental stress levels and their perception of the child's stressors are also significant. A caregiver's resilience is inversely related to both their stress and their perception of stress in their child. Interestingly, a father's depressive symptoms have a more pronounced impact on their parenting experiences, as indicated by higher reports of conflict, caregiver burden, and their child's perceived stress level, compared to mothers [99-101]. This research suggests a greater focus on family therapy, rather than individual parents or the child alone [84, 86, 89].

For children with divorced parents, mitigating parental conflict is essential. The tension and anger between parents can diminish their emotional capacity to provide a nurturing environment or responding to their child's needs [102]. Explaining the divorce situation to the child is also beneficial. These needs can be addressed through parent education and divorce education programs offered by community organizations. Additionally, extrafamilial support from teachers, extended family, clergy, and community resources demonstrating attention, warmth, ready availability, and respect for the child is essential. Factors such as a child's temperament, self-regulation, persistence, social responsibility, and independence from peer influence also play a role [103].

A research study on the parent-child interaction and resilient outcomes defines this relationship in terms of parental attitudes, involvement, and guidance, using Baumrind's heuristic distinction in parenting styles (authoritarian, overly permissive, authoritative). Parental attitudes that include caring feelings towards the child and appreciation of the child's abilities, lead to independence, self-esteem, coping skills, and reduced aggression [30, 68, 104]. Parental involvement by setting age-appropriate rules, consistent discipline, encouraging independence, and providing clear family routines boosts the child's self-esteem, internal locus of control, school adjustment and achievement, and greater resilience. Observing parents enjoying themselves or coping positively with life circumstances provides a model for the child to emulate. Resilient parent-child groups are characterized by congruent views of their relationship, underscored by effective parental communication [104]. Acknowledging the presence of an unseen, silent witness to family functioning in the household is also a powerful influence on child resilience as explored in the next section.

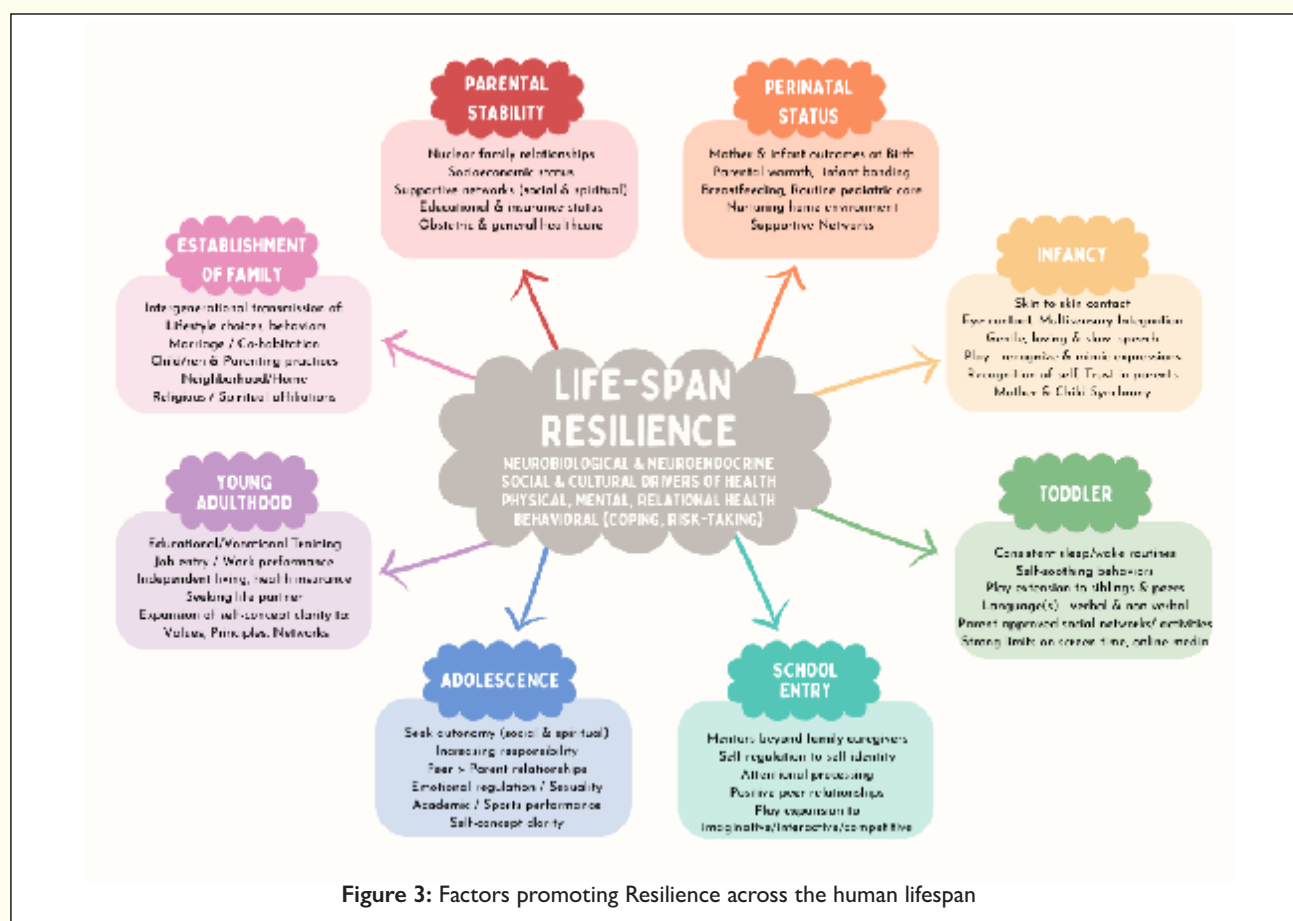


Figure 3: Factors promoting Resilience across the human lifespan

4.2. Spirituality

Spirituality and religion are well-known drivers of self-esteem and self-image showing abundant research on positive coping mechanisms associated with the cultural or personal interpretation of a higher being [105]. One study of Czech adults found that childhood trauma and difficulties in fostering were linked with a less positive image of God, especially in nonreligious participants [106]. Another study of homeless adolescents in Zimbabwe who believed evil spirits were controlling them, their morals and behaviors were tightly linked to evil spirits or super-natural powers, and most children had a negative self-image with negative implications on morality and social relations [107].

The impact of spirituality on resilience in children and adolescents is multifaceted and substantial. For younger children, the experience of spirituality is defined by their relationship with family and openness to new experiences. As they grow older, develop trust in their relationships, greater self-concepts, and their interpretations of reality through abstract thought, this plays a crucial role in their identity formation, self-esteem, social skills, and the ability to overcome adversity (or resilience). During school years, spirituality has a negative association with depression, substance abuse, delinquency, and criminality [108].

Following traumatic experiences, spirituality helps children to recover and redefine life's meaning, thus fostering resilience. It decreases PTSD symptoms by enabling individuals to rebuild their narratives based on healthy perspectives. Positive spiritual/religious coping strategies play a significant role in regaining a sense of control and combating feelings of helplessness, which is a common symptom of PTSD. These strategies include benevolent reappraisal, reinterpreting adverse experiences as lessons, learning forgiveness, fostering gratitude and generosity – all dependent on establishing a spiritual connection. Other methods such as active religious surrender, acknowledging what is beyond one's control, doing what's right and leaving the rest to God, and seeking spiritual guidance are also integral towards developing multisystemic resilience [109-111].

5. Conclusions

Establishing a common definition for resilience across different disciplines must acknowledge the changing ecological contexts from infancy to adulthood (Figure 3). Resilience, explored through interdisciplinary studies, is a metric to gauge an individual's reaction to and recovery from daily acute stressors and from cumulative chronic adverse conditions. This concept encapsulates the ability to reduce the negative consequences of ACEs or ELA without suggesting complete invulnerability to such events. Rather, resilience is measured by responses that fall within the normal expected variability of individuals facing acute, repetitive, and chronic stress with and without positive childhood experiences or nurturing environments. Ungar and colleagues suggest a bio-social-ecological interpretation of resilience with three characteristics:

- Equifinality – many proximal experiences can lead to variable, but equally viable, expressions of child development associated with well-being;
- Differential impact – children face different types and frequencies of ACEs, but their perception of resources available to overcome those risks, and the quality of these resources make proximal processes more or less influential in each child's development;
- Contextual and cultural moderation – different contexts and cultures provide access to different processes associated with resilience as it is defined locally [111].

In clinical settings, objective measures of age-associated biomarkers such as cortisol and oxytocin can monitor HPA-axis (dys)regulation to assess contextual risks vs. resilience. Developmental windows exist for HPA-axis maturation by 4 years of age with temporal peaks in cortisol levels observed perinatally and then again at school entry. In academic or social settings, behavioral adaptation or the way individuals form peer relationships can assess contextual risks vs. resilience. While age-dependent struggles are common, a key aspect is the eventual formation of the child's social networks with stable relationships. Relational health can be measured specifically through the challenges children face in their daily lives on a spectrum of behaviors to assess risk vs. resilience serially over time. Other disciplines may incorporate culturally relevant measures of normality, emotional regulation, self-esteem, or concepts of self-identity by measuring their associations with healthy coping strategies, self-esteem, or self-identity that define resilience. Future research must devote greater efforts to investigate the comparative efficacy of different approaches that can overcome adversity and promote resilience in children and adolescents, to ensure future survival and thriving of the human race.

Author Contributions: A.M.L. wrote initial drafts; K.J.S.A. wrote a revised draft; A.M.L., Z.C., C.R.R., and K.J.S.A. edited the manuscript; and A.M.L., Z.C., C.R.R., and K.J.S.A. created figures. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not Applicable

Informed Consent Statement: Not Applicable.

Data Availability Statement: No new data was created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

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