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Review Article

Akin to the Great Revolutions or Ages, the *Combinatorial Approach* for Preempting Genetic Diseases Requires the Confluence of Independent Scientific and Societal Developments Emerging from Synergisms Between Serendipitous, Planned and Natural Progressions Significantly Magnifying the Impact Over the Simple Sum of their Individual Components or Subfields

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Abstract

At least 65% of all diseases have a genetic component caused by the insertion of a genetic lesion into the genome as a consequence of the dysregulation of networks of genes for its maintenance. In the long term, a system for preempting these lesions in real time would have an unparalleled and positive impact on Medicine and Humankind. Including in ameliorating Human and Economic burdens on a scale of hundreds of trillions of dollars per annum. Assembling this system is indispensable for the Public Interest but subject to benign, if not optimistic, neglect. Many of the sciences, methods and elements of methods for initiating this assembly are available, or in development or conceivable by integrating and synthesizing an array of sub fields in the Life, Physical and Computational Sciences and Mathematics. The process depends as much on good planning as it does on serendipitous discoveries which represent the underpinnings of civilization. The assembly of the system for preempting genetic diseases is akin to those defining epochs or periods on a historical scale. Including the Renaissance, Industrial Revolution, Information Age, Space Age, Green Revolution and Biotechnology Revolution. All of which are far greater than the sum of their many components and vectors comprising of discoveries, inventions, explorations, planned progressions and of equal significance either serendipitous findings or unforeseeable consequences. All of which underlie civilization in all its dimensions. This is due to the simple reason that all of these vectors and components play associative, combinatorial, synergistic and complementary roles which together magnify the sum of the results of these progressive processes.

Keywords: Evolutionary & Mouse Genetics, Speciation; dysregulating Chromosome/Genome Biology; Mutome; Integration of Subfields of Life, Physical & Computational Sciences; Combinatorial Approach in Real Time Operations, Preemption of Genetic Diseases; Human, Health & Economic Costs & Burdens

The *LSINJ* has initiated an undertaking which is on an analogous scale with these historical periods, through the assembly of a system that is broadly defined as the *Combinatorial Approach* (*CA*). The *CA* predicts preemption of genetic disease lesions by systematization, surveillance and control of genetic networks maintaining and repairing the genome from which they escape, in real time (Figures 1-4) [1-30].

The processes underlying discoveries in the *CA* are categorically distinct in nature, scale, dimensions, depth, scope, objectives and predictable results from Precision and Translational Medicine. As well as from each of the landmark developments within any sub field of the Life, Physical and Computational Sciences. Examples of these landmark developments are exponential elevations in technical and scientific capacities in these sub fields represented by analytical systems or their discoveries. They include: single molecules in OMICs, single, embryonic and pluripotent Stem Cells, the Connectome, Graphene Biosensors, Photonics, Robotics, Nanobots, Subatomic Particles such as the Higgs-Boson, Supercomputers, Artificial Intelligence, Machine Learning, Nanobots and Mathematical Modelling, among others [1-30]. The *CA* would revolutionize the very paradigm of contemporary Medicine, from the management of pathological consequences of disease states to preemption of their causal genetic disease lesions [1-30].

The *CA* for preempting genetic disease lesions in real time, is an undertaking that is dependent on cooperation followed by collaboration and leadership encompassing both scientific and societal dimensions. The necessity for autonomy and independence of those with expertise within separate subfields has to be balanced by the leadership necessary to maintain the *CA* in overall development in a plausible direction. The *CA* simply cannot become viable, let alone meaningfully operational, when confined to the efforts of a single nation or a single generation [1-30]. Over the decades the *LSINJ* has played the role of integrating and synthesizing a wide array of sciences, leading more recently, to advocating for the conceptualization and initiation of the *CA* [1-30]. In addition to the sciences, as with undertakings of similar dimensions, all sectors of global society and governance making direct and ancillary contributions would be indispensable for the eventual realisation of the *CA*.

Should this undertaking eventually mature into a viable system, the potential impact of the *CA* on Humankind would be unparalleled in History.

Review

The unmistakable message in the above cartoon that was sent to us, implied that the *CA* for preempting genetic diseases lacks supporting evidence (data). Given the nature and dimensions outlining the enormity of the undertaking, that assertion in the cartoon not only states the obvious, but one which is only partly correct. Of greater significance it is irrelevant - a non sequitur for largely sociopolitical consumption!

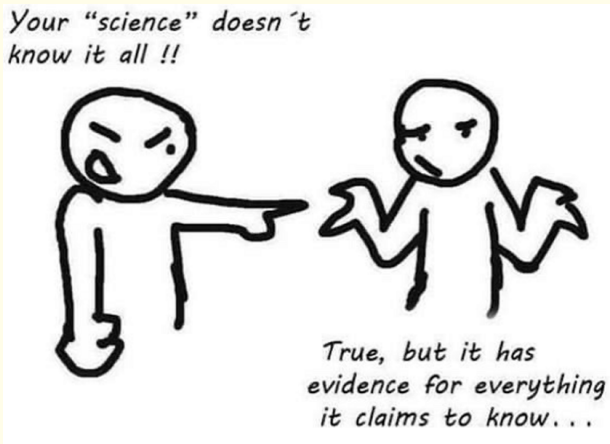

Figure a

First, even a cursory google search with limited search terms representing the relevant sub fields of the Life Sciences recovers hundreds of millions of hits and/or papers albeit those that are neither curated nor critically evaluated [1-30]. Furthermore, although these data entail the depth and focus necessary for elucidating mechanisms, beyond Models, they lack the physiological and evolutionary mechanistic relevance and so the integrative steps, synthesis and scope necessary for elucidating ongoing mechanisms that insert a genetic lesion into the genome. Let alone assembling a system for systematizing, surveilling and controlling networks of genes to preempt the insertion of genetic disease lesions and their respective pathological conditions [1,2,6,16].

Beyond Models, albeit tested in lower organisms, it is impossible to determine the relevant and ongoing mechanisms for genetic disease lesions that are inserted into human genomes, as by definition they are retrospective interpretations of the associated pathological conditions. Effectively eliminating any possibility of assembling systems for preempting them. However, this barrier can eventually be surmounted by applying the fundamentals of the *CA* that are worked out in mammals by applying a well-defined conceptual, scientific and technical repertoire. Including in the principal areas of genetics, OMICs, biochemistry, evolutionary genetics, molecular, cellular and developmental biology which by definition reduces

the choice to feral mice and mouse strains [1-16]. The objective of preempting genetic disease lesions and so the *CA*, is the dimension of Biomedical Research and Medicine with the single greatest impact and so necessary yet neglected. The *CA* is indispensable for the development and projection of the Scientific, Health and Economic Policies governing Humankind, with all its potential for amelioration of their respective challenges [1-30].

As shown below although there are daunting conceptual, scientific, technical, economic and ethical challenges to the *CA*, they are not insurmountable. It is the culture of Science that remains an insurmountable barrier, as has been experienced or quoted on by the likes of Drs. Albert Einstein, Barbara McClintock, Richard Feynman, J. Robert Oppenheimer and Andrei Sakharov [1].

The *CA* does not suffer from a lack of data for initiating the process but does clearly suffer from a lack of scientific initiative in integrating and synthesizing that data for preempting the insertion of genetic disease lesions in real time [1-30]. Under normal circumstances we would ignore the provocation represented by the above cartoon (Figure - cartoon). However there are far larger matters at play at the moment which would be endangered by a publicly unanswered innuendo. Albeit made by those who display compunctions when convenient [1-16]. This provocation likely originated from a Scientist with a long and checkered History revealed by a wide array of personnel. They ranged all the way from junior Scientists up to a Congressman who was a Central Figure in the Sociopolitical Pantheon of the United States. To put it mildly the standards of this Scientist did not quite meet the norms of the likes of Drs. Albert Einstein, Richard Feynman, Barbara McClintock, J. Robert Oppenheimer and Andrei Sakharov [1,3-6].

The current counterproductive paradigm in Medicine is exclusively confined to parameters collectively constrained by limited therapeutic interventions and as a result, their consequences. They are (i) exclusive confinement to post-mutational therapeutic interventions with no long term plan included for preemption of genetic disease lesions, (ii) recurrence of insertion of genetic disease mutations, their associated pathological conditions and expanding patient populations, (iii) post-mutational therapeutic interventions that are insufficient for rescuing even the extant global patient populations, (iv) this is so even when patients are afflicted by one of the diseases that is most technically amenable to therapeutic resolution such as sickle cell anemia (SCA), and (v) insertions of genetic lesions which cannot be followed, surveilled, controlled or preempted as they are largely based on models as well as retrospective interpretations, albeit those that either have some precedents in mechanisms, evolutionary orthologues or homologs that have been tested in simple organisms [1-16].

There are innumerable examples illustrating the paradoxes of great progress in post mutational therapy but with no relief in significantly greater limitations of expanding pathological conditions and patient populations. A biological system and pathological condition that is illustrative of this paradox is presented by human hemoglobin (HBB) complex for transporting O_2 and the disease Sickle Cell Anemia (SCA) associated with an A - T transversion in β-globin coding sequences. However there is no more rigorously and extensively characterized or highly developed biological system illustrating this paradox, than the human hemoglobin (HBB/HBA) complex for transporting O_2. Its limitations persist, despite its basic components being readily accessible and so enabling technical analysis. Over the past 100 years the HBB complex has been one of the most extensively and rigorously studied biological systems. Ranging from the atomic level structure of the protein complex, to genetic, epigenetic, molecular, cellular and developmental regulation. One that has culminated in the recent (gene/stem cell) therapeutic complementation of the A to T transversion in β-globin coding sequences that cause sickle cell anemia (SCA). Despite this cumulative accomplishment, all of the above limiting paradoxes (i) to (v) continue to apply to the highly developed HBB/SCA system! We have addressed these concerns and limitations emerging from the current largely counterproductive paradigm in Medicine [2-6].

The clearest and simplest demarcation of the progression of a genetic disease is represented by the stages *before* and *after* the insertion of the responsible genetic disease lesion into the genome (Figure 1-4) [2-6]. The stages before and during the insertion of the lesion include a Universe of contributing factors for which we have proposed the term *Mutome* (Figure 1-3) [1-16]. The *Mutome* may comprise of factors ranging from interactions at the atomic, molecular and cellular levels all the way up through to organismal, populational and environmental levels (multifactorial).

All therapeutic interventions in contemporary Medicine, including those represented by Precision and Translational Medicine or high resolution methods such as CAR-T, CRISPR/Cas9-Pam are post - mutational, therapeutic and *Analytical* methods. By definition they do not allow for the preemption of insertion of genetic disease lesions [1-16]. These methods cannot reveal (*Discovery* of) relevant genomic, physiological and evolutionary mechanisms

for the insertion of genetic disease lesions into the genome. This *Discovery* is only permitted by generating evolutionarily and physiologically relevant dysregulations including of Chromosome/Genome Biology.

This is made possible by the application of *Species Incompatibility* (*SI*) which is a fundamental *Principle of Evolutionary Genetics of Speciation* operating across the evolutionary spectrum [1-16]. *SI* occurs most often when the two contacting species are not co-adapted and retain the maximal numbers or degrees of divergent alleles [1-16]. This raises some questions about relevant quantitative and qualitative methods, governing factors or parameters and definitions in *Evolutionary Genetics of Speciation*, and *SI* which are beyond the scope of this mini-review but are extensively reviewed in the eBook from which it was extracted as well as the literature quoted in it [1,2,6,16-18]. A summarized version follows:

- The Contact Zone between species is defined by the apposed sectors of interaction between those species e.g. mice from two geographically separated zones,
- Interspecific allelic combinations within genomes of species geographically extending from the median to the borders of contact zones define Natural Hybrid Zones (NHZ).
- Introgression is the Evolutionary Genetics equivalent of backcross generations (N) of Classical Genetics and results from mating of F1 hybrids to either parental (P) species. The first introgressed (N) generation may or may not be productive (fertile or viable). The result of the latter mating reflects *SI* and is the consequence of *Reproductive Isolation* which therefore fulfills a requisite in the de novo formation of a new species.
- *Pre* and *Post Zygotic Reproductive Isolation*, as they imply occurs before and after the formation of a Zygote. *Prezygotic* mechanisms include habitat, mating seasons, environmental, gametic and behavioral isolation, while *Postzygotic* mechanisms include consequences of distinct F1 hybrids e.g. inviability and sterility and F2 hybrid "breakdown" [1,2,6,16-18].
- *SI* dysregulates chromosome and genome biology in NHZ as well as in laboratory matings and has been extensively documented; *de novo* matings required for *SI* based dysregulation are determined by initial contact between least co-adapted genes/genomes required [1,2,6,16-18].
- *SI* is reflected in Haldane's Rule - stating that interspecific combinations inviability and sterility occurs in heterogametic rather than the homogametic sex [1,2,6,16-18].
- Breeding structure of feral mice is restricted to *Demes* or territories comprising of a dominant male and upto 10 females. Therefore presumably driving intraspecies selection [1,2,16-18].
- In interspecific combinations, *SI* occurs as F1 hybrid sterility, F1 hybrid inviability and F2 hybrid breakdown in germlines or somatic tissues. This is the case, as these interspecific combinations of the least co-adapted alleles/genes/genomes represent maximal potential for incompatibility. It varies in magnitude between specific sectors of NHZ as well as with specific loci or chromosomes or segments of genomes and chromosomes [1,2,16-18].
- Are the numbers of mouse cells in the HMHZ or *NHZ* mouse cells/kb mouse genome sufficiently representative for covering the genome by '*Panning*' as opposed to e.g. for GWAS or Saturation Mutagenesis [1,2,16-18]?
- The short answer is Yes - by greater than several orders of magnitude relative to the average screen of λ libraries or GWAS [1,2,16-18].
    - We have addressed this issue by integrating the literature [1,2,6,16-18]. The European NHZ (or House Mouse Hybrid Zone) is the best characterized hybrid zone that is known. Based on the minimal and maximal characteristics of this NHZ (i) area in km^2, (ii) density of mice/km^2, (iii) average weight and cell numbers of mice normalized and extrapolated from humans, (iv) diploid mouse genome size of 6 x 10^6 kb/cell (v) the range of target cells in the European or *NHZ* mouse cells/kb of mouse genome it is (vi) calculated to range from = 9.11 x 10^6 *NHZ* mouse cells/kb (minimal) up to 2.54 x 10^8 *NHZ* mouse cells/kb (maximal) [1,2,16-18].
    - These are the numbers derived from a single NHZ of mice while at least 5 other NHZ of mice have been characterized on the European, Asian and American continents [1,2,16-18].
- Furthermore the World Health Organization (WHO) projects the global population of feral mice at approximately 20 billion [1,2,16-18]. This potentially increases the *NHZ* mouse cells/kb of mouse genome by a significant and exponential value.

- However, in at least some sectors of the European NHZ, 98% of the mice have been reported to be introgressed (backcrossed) for N generations and consequently alleles in their interspecific genomes are at least partially co-adapted [1,2,16-18]. Therefore potentially diminishing the magnitude of *SI* and correspondingly diminishing frequencies of dysregulations required for the *Discovery Phase* of the *CA. SI* is typically induced by initial or *de novo* interspecific contact and mating. However, an essential segment of the *CA* is based on genetic resolution and identification of the alleles responsible for dysregulated genes/genomes in candidate mice (*SI, NHZ*). In both the subsequent *Discovery* and *Analytical Phases* mating these candidate *SI*, (*NHZ*) mice with genetically defined mice exponentially increases the likelihood of both SI dependent dysregulation as well as its resolution and discovery of relevant alleles [1,2,16-18].

- As indicated above an additional large and indeterminate global population of mice bred by distinct breeding protocols yielding genetically defined or randomized genomes, is also available for genetic resolution of alleles inducing dysregulation. Highly defined and representative genomes or genetic backgrounds (including Inbred Strains, Recombinant Inbred Strains and Collaborative Cross strains) while random bred and out-crossed mice are also available for the genetic resolution of alleles inducing dysregulation of any trait [1,2,16-18].

- The collective feral, laboratory and commercial mouse populations represent a near infinite number of generations as well as permutations and combinations of mice that are available for the genetic resolution of alleles inducing dysregulation of chromosome and genome biology - an essential application in both the *Discovery* and *Analytical Phases* of the *CA*.

- Genetic lesions inserted as a consequence of *SI* followed up with '*Panning*' for disease (and other mutant) traits is the underlying basis of the *Discovery Phase* of the *Combinatorial Approach* (*CA*). In turn resulting in the systematization of genetic networks responsible for maintenance of the genome which when they fail, generate those insertions and traits. '*Panning*' is non-selected or non-targeted for a marker or a sequence or a phenotype. It is analogous to genome wide association studies (GWAS), chemical saturation mutagenesis, insertional and excisional mutagenesis Two-Hybrid Screens for interactors and epitope screening and conformational mapping of expression libraries.

When networks regulating any trait including chromosome/genome biology fail, genetic lesions, disease (and other) traits are either inserted or induced [1-16]. *SI* is expected to operate from atomic up to organismal, populational and even environmental (multifactorial) levels of interactions [1-16]. It is helpful to think of the analogy between *SI* (or 'A x B') mice and subatomic particle colliders [1-30]. With the difference that unlike collisions of subatomic particles, *SI* raises the frequency of, aberrant interactions between diverged interactors, and so the probability of dysregulation at all levels of diverged interactions. Of critical significance this dysregulation occurs withibn evolutionarily and physiologically relevant contexts and so permits the identification of ongoing causal molecules and mechanisms that are relevant to the insertion of genetic lesions into the genome at the organismal level [1-30]. To emphasize this point further, aberrant interactions leading to dysregulation are anticipated at all levels of divergent interactors from atoms to populations and environments [1-16]. This includes dysregulation of all components of Chromosome and Genome Biology consequently resulting in the insertion of genetic lesions into the genome [1-25]. In turn increasing the probability of *Discovery* of dysregulated products for analyses in the increasingly higher resolution *Analytical Phases* of the *CA* [1-30].

The underlying principle of *SI* in the application of discovering dysregulated traits in the *Discovery Phase* of the *CA* raises several questions. Specifically the i methods of dentification of those physiologically and evolutionarily relevant molecules and mechanisms responsible for the insertion of genetic lesions into the genome [1,2,6]. Many of the genes regulating the maintenance and repair of chromosomes and genomes are homologous or orthologous from bacteria to humans [1,2,6]. A large body of relevant work has already been done on a wide evolutionarily spectrum of organisms in natural field populations as well as in the laboratory. They include bacteria, yeast and fungal species, worms, fruit flies, fish, mice, rats and humans [1,2,6]. It is expected that they will be included in the *CA* either as test organisms or for reinforcement of results obtained in a relevant mammal [1,2,6]. However, given the extensive and well supported research on these Model Organisms the necessity is for the emphasis on the systematization of *in vivo* and organismal level regulation (or dysregulation) of mammalian Chromosome and Genome Biology. For a range of scientific and technical reasons the organism of choice for this purpose is the mouse [1-24].

Systematization of the mechanisms inducing failure of the maintenance of the genome are expected to lead to the institution of methods of surveillance and control of the networks for preemption of genetic disease lesions and traits in real time. This can only be attained when the *Discovery Phase* is applied synergistically and in conjunction with the *Analytical Phase* which includes high resolution contemporary methods.

Once the *CA* is functional it has to be extended into *Real Time Operations* (*RTO*). At its simplest *RTO* takes *afferent* input from the genome (molecules, cells, organisms) and produces *efferent* output from supercomputers to activate various *effectors* that are manifested as corrective actions for all dysregulation.

It is impossible to clearly demarcate segments of *Discovery*, *Analyses Phases* and *Real Time Operations* and their respective technological application or resolution in an undertaking such as the *Combinatorial Approach* (*CA*). For the simple reason that it has overlapping associative, synergistic, combinatorial, complementary and collaborative phases that are sub segments of *Discovery and Analyses* in the *CA* and the resultant *CA RTO*. However some level of development of *SI* based systematization of the networks of genes that maintain the genome clearly has to precede the assembly of systems for surveilling and controlling these genes. We refer to the above *SI* and systematization phase of the overlapping combinations as:

- *Natural Hybrid Zone* induced - *Spectrum of High Frequency Serendipitous Subversions of Chromosome Biology (NHZ -SHFSSCB)*
- The results of which would permit the eventual preemption of insertion of genetic disease lesions in real time (Figure 1-4) [1-30].
- We have already published a short synopsis extracted from an eBook (with references therein) explaining the *Combinatorial Approach* (*CA*) for preempting genetic disease lesions in real time *Real Time Operations* (*RTO*) whether in individual patients or general populations. The modified figures extracted from the eBook and links to the paper are listed below (links 1 > Figure 1-4; and links 1-5):
- www.LifeSciencesInstituteNJ.com
- Nallaseth FS, Shifting the therapeutic paradigm in medicine from post mutational (and pathological) intervention to preemption - a synopsis of the 'nuts and bolts'. https://www.lifesciencesinstitutenj.com/webinars-scheduled-delivered-by-lsinj-board-members-from-global-sites.; and ibid Full length eBook (in preparation).
- Nallaseth FS, LSINJ Webinar 17: https://www.lifesciencesinstitutenj.com/webinars-scheduled-delivered-by-lsinj-board-members-from-global-sites#h.iywoseh4jkp2
- Nallaseth FS, LSINJ Webinar 18: https://www.lifesciencesinstitutenj.com/webinars-scheduled-delivered-by-lsinj-board-members-from-global-sites#h.qmpsot4an5dm
- Nallaseth FS, LSINJ Webinar 21: https://www.lifesciencesinstitutenj.com/webinars-scheduled-delivered-by-lsinj-board-members-from-global-sites#h.6ucilopq1vgf

Figure 1 schematic representation of insertion of genetic disease lesions or assembly/functions of the Mutome in the choice between its dissolution and resolution.

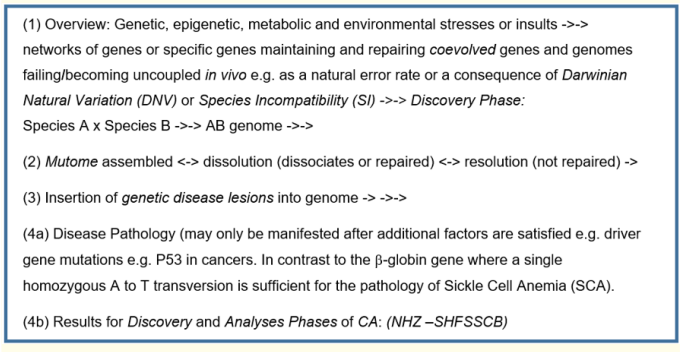

Figure 1: The above graphical schematics of the *Mutome* are self- explanatory. The proposals for the dissolution or resolution of the *Mutome* by the *CA* undertaking advocated by the *LSINJ* are based on over 150 years of developments in the Life, Physical and Computational Sciences and Mathematics [1-30]. The graphical schematic in the above figure is a preliminary proposal with limitations imposed by obvious physical and conceptual constraints. Of necessity with the emergence of results, an appreciation of the *Mutome* formed *in vivo* will be supplemented, enhanced, reinforced and modified by those who have the additional and necessary expertise in these and other Scientific fields. They will find relevance in later stages of the *CA* and take a natural place in

Species Incompatibility (SI) is expected to operate at all levels of interactions from atomic to organismal, populational and environmental (multifactorial level interactions). It is helpful to think of SI (or 'A x B') mice as biological analogs of Subatomic Particle Col-

liders of Physics [1-30]. With the difference that unlike collisions of subatomic particles, *SI* ostensibly raises the frequency of aberrant interactions between interactors and so the probability of dysregulation at all levels of diverged interactors. Conferring on this dysregulation as well as on resultant ongoing causal molecules and mechanisms the indispensable characteristics of evolutionary and physiological relevance [1-30]. This includes dysregulation of all components of Chromosome and Genome Biology [1-30]. Therefore increasing the probability of providing disregulated products from the *Discovery Phases* for subsequent or parallel analyses in the *Analytical Phases* of the *CA* (Figures 2 and 3).

Figure 2 potential pathways/overlaps and components of the *Combinatorial Approach* (*CA*) - *Discovery and Analytical Phases*.

complementary, serendipitous and

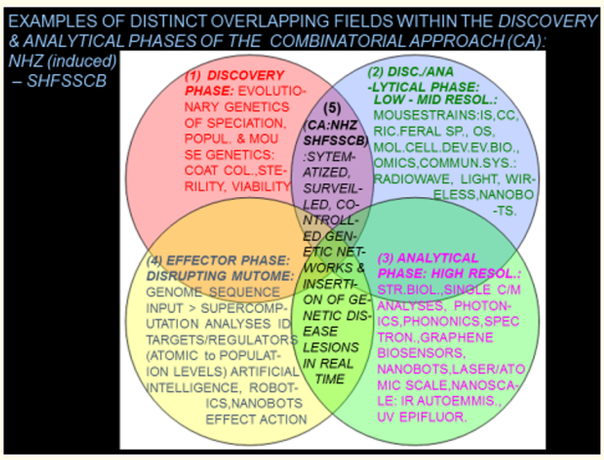

Figure 2: In the above graphical schematics all the sectors and their respective *Discovery* or *Analytical* Methods are color coded and self-explanatory. *NHZ* induced - *SHFSSCB* in the projected *Discovery* and *Analytical Phases* of the *CA* and upto the dissolution of the *Mutome* are presented in the 4 sectors (Phases 1 - 4) of the Venn Diagram. These 4 Phases have headings categorizing their broad structure and function respectively representing the (1) *Discovery Phase*, (2) *Discovery/Analytical Phase*: Low Resolution, (3) *Analytical Phase*: High Resolution, and (4) *Effector Phase*: Disrupting *Mutome*. The methods and technologies represented in each sector are selected from a widerange that are relevant, interchangeable and replaceable but designed for methods and sciences of the *Discovery* and *Analytical* phases of the *CA*. The central sector (5) of overlap between all 4 independent sectors (1 - 4) represents the combinatorial, associative, synergistic, complementary, serendipitous and unexpected consequences in addition to natural or planned projected plans that lead to the *CA* and the disruption of the *Mutome* (5) *CA: NHZ-SHFSSCB* This result borders on testing the *Real Time Operational* (*RTO*) of the *CA*. The roles or principles of *SI, Panning* analogies, assembly and other details are discussed in the text.

Figure 3 potential schematic of *Real Time Operations* (*RTO*) of *CA* first tested in mice and then applied to healthy individuals, patients and global populations.

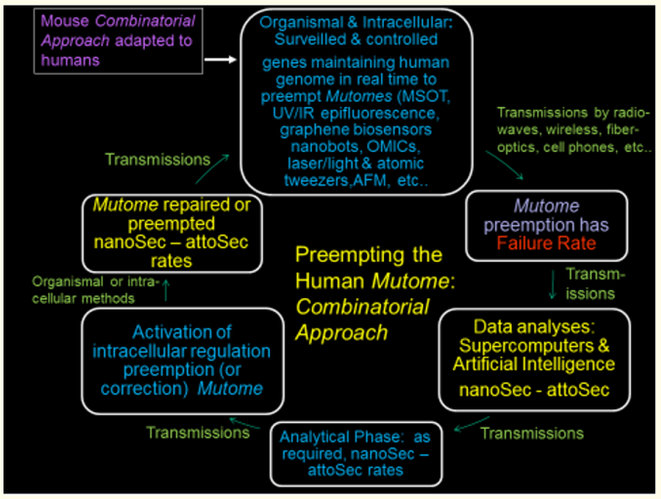

Figure 3: The above cyclical and graphical schematics are color coded and self explanatory. The stages of the *CA* are followed by its extension into *Real Time Operations* (*RTO*) in mice. This is then followed by analogous stages of *RTO* in humans, individuals, patients and populations. The *CA* undertaking advocated by the *LSINJ* is based on over 150 years of developments in the Life, Physical, Computational Sciences and Mathematics [1-30]. The above graphical schematic is a preliminary proposal with limitations imposed by obvious physical and conceptual constraints. Of necessity, with its development, the *CA* will be supplemented, enhanced, reinforced and modified by other Scientific fields They will find relevance in later stages and so take a natural place in its progression. These fields and their methods are applied for analytical elucidation in the subsequent *Analytical Phases* of the *CA* before being tested for *Real Time Operations* (*RTO*) in mice and humans [1-30]. Of necessity with the emergence of additional results, an appreciation of the *CA RTO* will be supplemented, enhanced, reinforced and modified by those Scientists and other personnel who have the additional expertise in these and otherScientific fields. They will find relevance in later stages of the *CA RTO* [1-30]. These contributions will be inserted either as independent modules or dove-tailed into ongoing developments of the *CA RTO*. This process is much like the insertion of distinct preassembled modules into the International Space Station (ISS) as it was being assembled.

Figure 4 summary of the basic principles of the *CA RTO* for preempting genetic disease lesions.

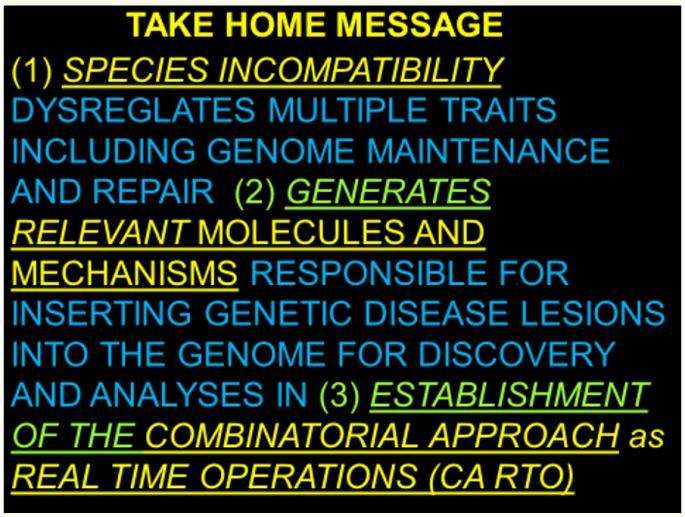

Figure 4: The graphical schematics of Figure 4 are color coded and self-explanatory. They project the landmark stages and products defining the *CA* that are illustrated in figures 1 - 3. Essentially illustrating the application of *SI* for elevating the probability of generating *Mutomes* and dys-regulated but relevant products and mechanisms in the *Discovery Phases*. These are applied for analytical elucidation in the subsequent *Analytical Phases* of the *CA* before being tested for *Real Time Operations (RTO)* in mice and humans to yield *CA RTO* [1-30].

To re-capitulate, proposals for the dissolution or resolution of the *Mutome* by the *CA* undertaking advocated by the *LSINJ* are based on over 150 years of developments in the Life, Physical and Computational Sciences and Mathematics. The graphical schematic in the above figure is a preliminary proposal with limitations imposed by obvious physical and conceptual constraints. Based on the *Evolutionary Genetics Principle of Speciation* established as *Species Incompatibility* (*SI*) there is a formation of the *Mutome* to be dissolved/resolved for detection in the *Discovery phase* of the *CA*. *SI* conceivably operates from atomic level to organismal, populational and environmental (multifactorial) level interactions. It is helpful to think of *SI* (or ''A x B' genomes) mice as being analogous to Subatomic Particle Colliders of Physics [1-30]. With the difference that unlike collisions of subatomic particles, *SI* ostensibly raises the frequency of aberrant interactions between any diverged interactors and so causes dysregulation at all levels of diverged interactors in contexts that are evolutionarily and physiologically relevant [1-30]. This includes dysregulation of all components of Chromosome and Genome Biology with results and products for *Discovery* and *Analyses Phases* of *CA* that are summarized as (*NHZ -SHFSSCB*) [1-30]. Therefore increasing the probability of providing dysregulated products in the *Discovery Phases* for analyses in the subsequent *Analytical Phases* of the *CA*. This *Discovery* is only permitted by generating evolutionarily relevant dysregulations including of Chromosome/Genome biology. *Species Incompatibility* (*SI*) is the underlying basis of the *Discovery Phase* of the *Combinatorial Approach* (*CA*) which is followed with '*Panning*' for disease (and other mutant) traits; and therefore the systematization of genetic networks responsible for maintenance of the genome which when they fail, generate those traits. *Panning* is non-selected or non-targeted for a marker or a sequence or a phenotype. It is analogous with genome wide association studies (GWAS), chemical saturation mutagenesis, insertional and excisional mutagenesis, Two-Hybrid Screens for interactors and epitope conformational screening. When networks regulating Chromosome/Genome Biology fail, genetic lesions are inserted, disease (and other) traits are induced [1-16]. Of necessity with the emergence of additional results, an appreciation of the *CA* will be supplemented, enhanced, reinforced and modified by those who have the additional expertise in these and other Scientific fields that will find relevance in later stages of the *CA* [1-30]. These contributions will be inserted either as independent modules or dove-tailed into ongoing developments of the CA. This process is much like the insertion of distinct preassembled modules into the International Space Station (ISS) as it was being assembled.

Both the strength and challenge to the *CA RTO* emerges from the availability of the vast and relevant literature and diversity of technology made available by Scientists in the Life, Physical and Computational Sciences and Mathematics for initiating the *CA RTO* [1-30]. However, the challenge as shown by History is presented in melding all the different cultures, professionals, scientists and technologists generating this data having to work together effectively in assembling a viable and functional *CA RTO*. The inherent complexity is one of balancing the necessity for autonomy permitting the application of expertise within multiple subfields, with retention of the overall developmental trajectories and pathways of the *CA RTO*. Additional administrative and scientific challenges are represented by the necessities of unhindered communications as well as

the necessary balance between depth and focus with breadth and integration of scientific applications. The former combination is indispensable for discovering mechanisms and therapeutic intervention while the latter combination is indispensable for ensuring the physiological and evolutionary relevance of mechanisms and pathways that are discovered. These divergent choices demand the leadership of Scientists who are not only at the pinnacle of their respective sub fields but also recognize their societal dynamics and obligations. As did Drs. Albert Einstein, Richard Feynman, Barbara McClintock, J. Robert Oppenheimer and Andrei Sakharov!

Challenges to initiating the *CA RTO* for preempting genetic diseases

There are persistent, if superficial and ill-considered, questions directed at the scientific viability of the *CA RTO* undertaking advocated by the *LSINJ*. This is so despite repeated rebuttals and clarifications of the necessity as well as the dimensions of the enterprise. One which is foundational for the sustainability of both global Health and Economic interests. However, a continued rote repetition of questions that have been addressed repeatedly is tantamount to disinformation! In preempting genetic disease lesions, the *CA RTO* is not only scientifically plausible, it remains the core, legal obligation, and so a non-discretionary objective of the *LSINJ*. The latest rebuttals of these persistent, superficial and ill-considered questions directed at the *CA RTO* are sketched below [1-30].

Although the necessity for development of the *CA RTO* is indisputable, in the *LSINJ* we have also emphasized the necessity for retaining the full repertoire of alternative current therapeutic interventions and research developments. Including all of the contemporary approaches that are extant, highly successful in Medicine and even recognized with the award of Nobel Prizes such as CAR-T and CRISPR/Cas9-Pam [1-30]. They are neither mutually exclusive nor in competition with the *CA RTO* in any manner that is extant or foreseeable!

The *CA RTO* represents long term therapeutic intervention which attempts to break the cycle of recurrence of genetic diseases, including the most intractable and dehumanizing diseases with the resultant elevation of global patient populations. The *CA RTO* promotes the long term Public Interest by relieving counterproductive consequences of the paradigm in contemporary Medicine. It preempts genetic disease lesions, the recurrence of pathological conditions, intractable disease states and untenable economic costs [1-16]. However, in contrast to the *CA RTO*, the current paradigm in Medicine is indispensable for immediate and critical therapy of patient populations. Even if these current methods are only transitional and perpetuate the recurrence of pathological conditions they will remain essential for the foreseeable future [1-16]. Nothing should be permitted to disturb development and application of either the *CA RTO* or current therapeutic or extant methods [1-16].

The latest of four decades of attempts, at discrediting the work leading to the *CA RTO* including the science on which it was anchored, were directed by sources external to the *LSINJ*. They incorrectly asserted a lack of data for supporting the *CA RTO* and made alternative but questionable proposals (cartoon) [1-30]. Searches (Google) of some relevant search terms in the subfields of the Life Sciences, not including the Physical and Computational Sciences, returned tens or hundreds of millions of 'hits' and/or papers [1-30]. Albeit neither critically evaluated nor vetted nor curated for overlapping subject matters they represent a substantive literature. Therefore these 'hits' or papers, by their sheer volume, still reveal the magnitude of data or results in the literature supporting the experimental basis and the fundamental elements of the *CA RTO*. Making most of these publications relevant to initiating the establishment of physiologically and evolutionarily and genomic or chromosomal mechanisms for insertions of genetic disease lesions into the human genome and so the *CA RTO* [1-30].

However, elements of this assertion regarding the lack of supporting data, are discernable in this vast literature. Although there are tens or hundreds of millions of 'hits' or papers in relevant fields, beyond models, they have never been integrated or synthesized, so as to elucidate mechanisms of ongoing insertions of genetic disease lesions into the genome. This integration and synthesis of results is represented in the *Discovery* and *Analyses Phases* of the *CA RTO* [1-30]. It is indispensable for revealing, surveilling, controlling and preempting the insertion of a genetic disease lesion into a gene or the genome. It is this integration and synthesis of results in combination with further experimental methods that are adaptable and that can be expanded through collaborative but guided and measured investigations across the scientific and mathematical fields that is advocated by the *LSINJ*. The *LSINJ.* However, while collaborating the *LSINJ*, must retain its independence to maintain credible advocacy for the *CA RTO* and so uphold the Public Interest in it [1-30].

Other assertions are insistent perspectives on the universal applicability of Mathematical Modelling and Precision Medicine across the sciences. The proposal was for the exclusive application of Mathematical Modelling as the preferred approach or solutions to most if not all undertakings in the scientific process. Mathematical Modelling has known limitations whether in predicting the folding of single RNP molecules or in predicting complex Weather Patterns [1,2,6,26-30].

By taking into consideration the most advanced technological capability necessary for the *CA RTO* the above questions as well as the limitations of current available choices are readily discerned or emphasized [2,6,26-30]. Predicting all the variations of nucleotides that would emerge from a single calculated run of sequencing genomes of the global human population emphasizes the magnitude of the technical barriers for the Mathematical Modelling proposal. Ignoring all the known scientific and technical variables, a single run of sequencing the global population of human genomes with the fastest Sequencers would result in the calculated yield of 1.67×10^{33} nucleotides at the minimum rate of 2 hours/run. These sequence data could only be derived with the fastest current sequencers, Ion Torrent and PacBio, and the associated Supercomputers. These data in themselves may present an insurmountable analytical challenge to Mathematical Modelling as well as to current Supercomputers and by extension to *CA RTO* [1,2,6,26-30].

Given the sheer volume of sequence data (Petabytes/Petaflops) it may not even be possible to capture, store and analyze genomes at necessary rates and resolution with the Supercomputers that are currently available for application in the *CA RTO* [26-30]. Ignoring variables and sketching the complete input/output loop of the *CA RTO* identifies the minimal number of steps required for developing nucleotide level resolution of the global population in the *CA RTO* (Figure 2 and 3). These include acquisition of the *afferent* input represented by the biochemical signal of sequences and errors in genomic DNA. One that is read from the template after unpacking folded chromatin of all cells/individual or patient in the population under study. Followed by the conversion of the biochemical signal to a digital or optical signal for communication to Supercomputers and subsequent analyses of the input. A critical challenge is presented by the necessity of refolding the unpacked chromatin. Followed by the appropriate corrective *efferent* output and activation of *effectors* from Supercomputers communicated by the reversal of the process.

The objectives of the *CA RTO* include significantly decreasing the mutational rates of the mammalian genome attributable to all dysregulations of Chromosome and Genome Biology. However, a challenge would be presented by even restricting the *CA RTO* to published error rates of the replicating mammalian genome to 1.1-12.4×10^{-9} substitutions per site per year.

This input/output loop of *CA RTO* signaling activates the response of preempting insertion of genetic lesions. It is conceived that the induction of a spectrum of well-known repressors or activators operating at the atomic (structural biology), molecular, cellular and organismal level with biochemical or physicochemical intermediaries could be directed to sequence(s), loci, chromosomes or genomes either at risk for insertion or ones in which a genetic lesion is inserted [1-30]. In this scheme it is not implausible for the additional deployment of high rate and resolution technologies operating at microsecond to attosecond (10^{-6} to 10^{-18} second) range such as Biophotonics, Optonics, Phononics, Nanobots, Graphene Biosensors etc. as functional mediators (Figure 2 and 3) [1,2,6,26-30]. The basis of this requirement of rate and resolution as well as the extant and developing technology is presented below.

RNase A which is recognized as having the perfect enzyme substrate associations represents the maximal rate constant of 10^8 $M^{-1}s^{-1}$ [2,6]. Based on the minimal steps in the above *CA RTO* loop and the maximal possible rate of the steps extrapolated from the RNase A reaction with its substrate, the functional rates of Ion Torrent and PacBio Sequencers are too low by a factor ranging from 10^{-6} seconds (microseconds) to 10^{-18} seconds (attoseconds). However, in a positive development, it has been shown that attosecond time frames have been attained in current applications of the Life and Physical Sciences (Figure 1-4) [1,2,6,26-30]. In fact electronic systems and filters that are currently available can capture a subatomic particle existent at the smallest measurable unit of time is 10^{-21} second (yoctosecond). This is on the order of the Half Life of the Higgs-Boson particle (1.6×10^{-22} sec) which has a mass that is 3-4x greater than a Photon of light. The existence of the Higgs Boson particle was finally confirmed in the Large Hadron Collider (LHC) [6,26-30]. There is no regulatory quantification or qualitative measurement in current biomedical research that requires anything like this resolution of space and time.

However, current developments in Photonics, Spectronics and Phononics suggest that light based Sequencers can potentially be developed that would eliminate many if not all of the rate limiting steps of Ion Torrent and PacBio Sequencers [1-30]. The principles of light based sequencers are embodied in IR autoemmissions, UV epifluorescence, laser and UVX spectra, optoacoustic tomography (MSOT), coupled with Graphene Biosensors deployed as signal Amplifiers and Supercapacitators [1,2,6,26-30]. These light based sequencers would accelerate rates, magnify sensitivity and elevate resolution of current Sequencers by orders of magnitude [1,2,6,26-30].

Some Sequencers for limited *in vivo* whole organism applications (21 - 600 nucleotides) such as 'Bar Code Sequencing' of single mRNP molecules and transcriptomes are already in use and could potentially be modified for applications to sequencing the genome in the *CA RTO* [6,26-30].

Associated and significantly greater computational power represented by Quantum Computers are also under development [2,6,30]. Operational Principles of Quantum Computers based on Lasers and Mirrors are reportedly responsible for this elevation in speed [6,30]. They will eventually go online and reinforce the *CA RTO* [2,6,30]. In addition the necessary and associated cybersecurity and analytical capacity of Quantum Encryption and Artificial Intelligence (AI) is also under development [2,6,30].

As an illustrative example, of the magnitude of operations and the development of new analytical technology are also presented. Radio wave signals from Deep Space acquired by the Square Kilometer Array of Radio Telescopes (SKA) generate Petabytes of data. To quote they require: 'analyses by Super-computers operating at 100 petaflops/second (one hundred thousand million floating point operations per second of raw processing power), to generate 600 Petabytes of data per year. To store this data on an average 500 GB laptop, you would need more than a million of them every year [6,26,27]. Significantly, greater capacity and faster Quantum Computers are also under development [6,30]. Operational Principles of Quantum Computers based on Lasers and Mirrors are reportedly responsible for this elevation in speed [6,30]. They will eventually go online and reinforce the *CA RTO*.

Several other technological systems, relevant to *CA RTO* have also been developed recently. These include Microfluidics and Optogenetics based microscopic visualization of the docking of regulatory proteins or enzymes on DNA sequences or sites of single cells, enabling the visualization of execution of their specific functions in real time [1,2,6]. An illustrative example is the microscopically visualized docking of the biochemically defined and fluorescent mismatch repair protein MutL on presumptive but biochemically predicted error sites of replicating DNA sequences in dividing single *E. coli* cells [1,2,6]. This system has projected applications even in Zebra fish (*Danio rerio*) [1,2,6]. It is not inconceivable to entrain such technologies into the *CA RTO*.

Another point of confusion was that of Precision Medicine being an umbrella system over the *CA RTO*. Unlike *CA RTO* Precision Medicine is restricted to therapeutic intervention *after* the insertion of genetic disease lesions - which perpetuates their recurrence as well as that of patient populations!

Although they fulfill necessary immediate if transitional functions both Translational and Precision Medicine as well as Mathematical Modelling neither reveal relevant intermediate molecular nor cellular mechanisms for inserting genetic disease lesions into the genome in real time. This is as indispensable for preemption of genetic disease lesions as is 'functional remaining the indispensable moiety of functional genomics' [2-6,9].

All post mutational therapeutic interventions are ineffective in breaking the perpetuation of intractable or recurrent cycles of pathology. Only the *CA RTO* can eventually attain this objective by bringing the necessary shift in the contemporary paradigm of Medicine from managing pathological consequences of diseases to preempting the insertion of their causal genetic disease lesions [1-30].

However, in addition to those factors that we have already identified, there are additional reasons that are responsible for the current counterproductive paradigm in Medicine. They arise from scientific 'dogmas' or Scientists who 'suffer from the prejudices of their generation' as was respectively asserted by the Nobel Laureates Barbara McClintock and Albert Einstein [1]. They include exclusive focus on high throughput, high velocity, high precision, and high resolution experimentation even when they can be irrelevant either mechanistically or for the larger scientific conceptual and societal objectives of the investigation in question. As for example in investigations that are dependent on the relevance of physiological, genomic and evolutionary contexts of mechanisms and their

Discovery e.g. chromosome mechanics, and *CA RTO* for preemption of cancer and AD as opposed to dSLAM, GCR and CRISPR/Cas9 - Pam which have predominantly analytical applications [1-30].

Another example, is represented by compulsions making research investigations exclusively limited to narrow, depth and focus, as opposed to also including integration and synthesis, breadth, scope, synthesis and integration of sub fields. This 'dogma' is enforced regardless of the necessity for engaging both sets of approaches or dimensions. The former generates mechanisms that are indispensable to establishing reality as well as therapeutic interventions even if they are transitional and ameliorative. While the latter is necessary for functional relevance in organisms and patients with the emergence of results and systems that could diminish post-mutational therapeutic interventions if not eliminating their necessity [1-30]!

As public or private funding for research is heavily, if not exclusively, directed to the former approach, the latter equally necessary approach is selected against. This leads to and meets the requisites for successful scientific and university faculty careers. However they are secured at the expense of necessary and relevant approaches and so contributions to the Public Interest. All of the former are driven by quaint noxiums associated with requirements for funding. These include (i) 'hypothesis driven' which assumes all knowledge for experimental investigation that is known is sufficient for meeting scientific or societal objectives, (ii) 'publish or perish', which is self - explanatory, (iii) budgetary justification with 'dollars per square foot of lab space' and (iv) the compulsive exclusion of serendipity which is universal in its applications in civilization with its significance in the sciences best illustrated by the discovery of Penicillin [1-16]. As a result these and other dogmas perpetuate the counterproductive paradox of exclusive management of pathology in Medicine and its consequences. Namely, the absence of diminution of the incidence rate of intractable pathological conditions and amplification of sizes of patient populations. The literature as well as the contemporary Paradigm in Medicine reflects this paradox [1-30].

As emphasized by these selective examples as well as by the spectrum of the vast literature in the Life, Physical and Computational Sciences the barrier to the *CA RTO* is neither conceptual nor scientific nor technical nor technological nor physical nor computational capacity [1,2,6,26-30]. Examples of exponential elevation of technical and scientific capabilities in these sub fields include [1-30].

- Single molecule analyses in OMICs; CHIP and Epigenomics;
- Mapping the Connectome or Replication/Transcription Domains; and sequencing the Genome, Proteome, Transcriptome and Epigenome or applying CRISPR/Cas9-Pam;
- Analyses of single, embryonic and pluripotent Stem Cells; chimeric antigen receptor T cells (CAR-T)
- Applications of Graphene Biosensors; Multi Spectral Optoacoustic Tomography (MSOT); Photonics; Phononics; Spectronics; Robotics and Nanobots *in vivo* visualization of cellular and whole organismal functions; Optogenetics; Microfluidics;
- Mass Spectrometry Approaches: MALDI-MS, Laser Capture Dissection – LC-MS/MS-TOF;
- Artificial Intelligence and Machine Learning;
- Confirmation of the existence of the Subatomic Particle Higgs Boson, in the LHC and the analyses of Radiowaves from Deep Space (to be) acquired with SKA radiotelescopes in combination with the Computational Sciences including Supercomputers, Quantum Computers and Quantum encryption
- Mathematical Modelling.

These recent and landmark developments are either currently operational applications, under development or can be potentially developed for application in the *CA RTO* where they can act synergistically to maximal effect and impact leading to the preemption of genetic diseases [1-30]. In isolation, these landmark developments are neither currently relevant for the *CA RTO* nor can they be potentially developed for preemption of genetic disease lesions [1-30].

The most significant barrier to the *CA RTO* is represented by the absence of any clarity or attempted clarity in elucidating either the regulation or the dysregulation of relevant biological mechanisms for inserting genetic disease lesions *in vivo* [1,2,6]. It is the necessary area of initiation and concentration that would permit the maximal progress in the realization of the *CA RTO*. Consequently, bringing the necessary shift in the current Paradigm in Medicine

from management of pathological consequences to preemption of the insertion of their causal genetic disease lesions [1-30].

This resistance to the *CA RTO* and the *LSINJ* is directed from the highest levels of science. They represent those who in Albert Einstein's and Barbara McClintock's words respectively 'suffer from the prejudices of their generation' and 'dogma' [1]. They were directed at the scientific basis of the *LSINJ* for decades before the restructured *LSINJ* was established in 2018. We are glad to revisit this as another documented discussion, provided that it is based on data, results, history and thoughtful discussion embedded in the principles of the Life Sciences. However so far rote repetition or outright disinformation is inescapable [1-30].

When should the *CA RTO* initiative be launched?

Current technical limitations e.g. of real time and single molecule Sequencing and the associated Computational capacity for analyses, do raise pertinent questions for the *CA RTO*. Namely when or whether the undertaking should be initiated. Should the *CA RTO* be initiated: (i) at all or (ii) at some distant future period after the development of applications with the requisite magnitude and resolution of analytical power or (iii) immediately? The short answer is (iii) immediately and it is informed by the recent development of the above technologies. Some that are already developed, others that are under development and still others that are predicted and conceivable. Assembling the necessary level of relevant *Analytical* capacity and sophistication in the *CA RTO* is dependent on extensive preparatory work with lower resolution *Discovery* methods and their results. Furthermore, the *CA RTO* is critically dependent on associative, synergistic, complementary and combinatorial associations between natural, planned and synergistic progressions as well as serendipitous and unanticipated consequences. All of which are rate and resource limiting and time intensive. Translation into amelioration of the current health and economic crises, as well as in the cumulative effort to rescue millions of lives in the distant future, is dependent on the immediate initiation of the *CA RTO* with little time to spare.

Conclusion

The *LSINJ* has initiated the undertaking of the *CA RTO* which is on the scale, complexity and positive (or negative) impact attributed to all the great Revolutions and Ages of History. Members of the *LSINJ* foresee that the *CA RTO* undertaking will permit the preemption of genetic disease lesions through systematization, surveillance and control of genetic networks maintaining and repairing the genome in real time (Figure 1-4 [1-30]. Cumulative processes underlying discoveries in the *CA RTO* are categorically distinct in scale, depth, scope and impact from Precision and Translational Medicine. As well as from those landmark developments within any of the sub fields of the Life, Physical and Computational Sciences and Mathematical Modelling, which are far less effective when they are taken in isolation. The *CA RTO* would revolutionize the very paradigm of contemporary Medicine, from the management of pathological consequences to the preemption of their causal genetic disease lesions in real time.

The *CA RTO* undertaking advocated by the *LSINJ* is based on the cumulative concepts and results emerging from over 150 years of conceptual and technical developments in the Life, Physical, and Computational Sciences and Mathematics. Of necessity, with its progressive development, the *CA RTO* initiative of the *LSINJ* will be supplemented, enhanced, reinforced and modified by those who have the expertise in these initial and other additional but supplementary scientific subfields. They will find application and relevance in later better developed stages of the *CA RTO* with its increasing analytical sophistication. Consequently taking a natural place in the progression of the *CA RTO*.

In addition, for the *CA RTO* enterprise to become viable, operational and sustainable, it will necessitate the engagement of all sectors of Society, including Citizen - Scientist and those Authorities in Governance. It is anticipated that they will play a role in making direct as well as ancillary contributions. This dimension of the *CA RTO* initiated by the *LSINJ* parallels equally large, scientific undertakings of distinct orientations, that are in the Public Domain, including NASA, DARPA, NIH, NSF, NCI among others.

The *CA RTO* is an undertaking for preempting genetic disease lesions in real time that is unparalleled in History. By its very nature the *CA RTO* is dependent on cooperation followed by collaboration and initiatives among global partners and representative, that is inherently challenging. As well as leadership that goes beyond its Scientific acumen to understand its Societal obligations increasing the challenge. Akin to that which has been demonstrated by Drs. Albert Einstein, Richard Feynman, Barbara McClintock, J. Robert Oppenheimer and Andrei Sakharov among others [1].

The *CA RTO* can neither become viable nor operational when limited to the contributions of any single nation or generation. The challenge for the *CA RTO* is to balance the inclusion of necessary independence of collaborating global entities with the equally essential impartment of direction and purpose of development delivered by Scientific, Governmental and Societal Leadership. Over the decades the *LSINJ* has played a spectrum of roles in advocating for the conceptualization, exploration and initiation of the *CA RTO* and will continue doing so.

Prospects

In the long term a system for preempting genetic disease lesions in real time would have an unparalleled and positive impact, on Humankind at large. It would be one that would extend far beyond the confines of Medicine. Institutionalizing the *CA RTO* system is vitally essential to the Public Interest or the Common Good. However the administrative reality in science and governance, is that the fundamental process on which it acts, the insertion of genetic disease lesions, is subject to benign, if not optimistic, scientific neglect [1-26]. Many of the concepts, sciences, technologies and methods or their elements for initiating the *CA RTO* are either already available, or in development or can conceivably be developed through the confluence of future discoveries that are highly predictable [1-26].

The *CA RTO* is an undertaking that is dependent on the integration and synthesis of an array of sub fields in the Life, Physical and Computational Sciences and Mathematics [1-26]. However, development and deployment of the *CA RTO* depends as much on progressions resulting from careful planning as it does on serendipitous discoveries (as well as unforeseen consequences) which are the underpinnings of civilization. The emergence of the *CA RTO* system for preempting genetic disease lesions is akin to those defining epochs or periods on a historical scale [1-30].

Progressions in the periods of History represented by the Renaissance, Industrial Revolution, Information Age, Space Age, Green Revolution and Biotechnology Revolution are examples for the *LSINJ* in its advocacy for the *CA RTO* [1-26]. All of which are far greater than the sum of their many vectors and components comprising of discoveries, inventions, planned and natural progressions as well as serendipitous findings and unforeseen consequences. This is the case, for the simple reason that all of these vectors and components play associative, combinatorial, synergistic and complementary roles which together magnify the results of these progressive processes [1-30].

Beyond ameliorating the impact of human costs, as well as those of healthcare the *CA RTO* would mediate a shift from the current Paradigm of Medicine that would have a ripple, wave and larger effect in relieving the pressures of unsustainable global socioeconomic burdens [1-16]. Independent studies have returned conservative estimates of annual healthcare costs in the sum of hundreds of trillions of dollars [1-16]. Ameliorating the global healthcare burden with the *CA RTO* would release resources, permitting ameliorative socioeconomic measures or interventions and resolution of conflicts on a global scale. In turn permitting the management, if not the elimination, of some of the most egregious of contemporary sociopolitical injustices on a global and historical scale!

However, all of this can only materialize if the *CA RTO* undertaking is directed by those, who meet the broad outlines of a quote by Dr. Albert Einstein. 'A knowledge of the historic and philosophical background gives that kind of independence from prejudices of his generation from which most scientists are suffering. This independence created by philosophical insight is - in my opinion - the mark of distinction between a mere artisan or specialist and a real seeker after truth" [1,2,6].

We have good reason for sharing this concern.

Should it ever mature into a viable system the potential impact of the *CA RTO* on Humankind would be unparalleled in History.

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