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Short Communication

Parallels between Existential Consequences of Decisions Enforcing the Current Paradigm in Healthcare to the Exclusion of *CA RTO* and those Made in the Cold War

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Comparative evaluations of key policy decisions detracting from and confronting the conceptual necessity for initiating the *combinatorial approach in real time operations* (*CA RTO)* for preempting genetic disease lesions including the *Mutome* are summarized here (Figures 1-4), [1-3]. The harnessing of *Evolutionary Genetics of Speciation (EGS)* and specifically '*Hybrid Incompatibility (HI)*' and its wider generational manifestation '*Species Incompatibility (SI)*' in combination with the resolving power of contemporary methods, permits the elucidation and preemption of mechanistically relevant failures of networks of genes that maintain genomes as e.g., with *CA RTO*. *EGS* and '*Species Incompatibility'* can permit the single generational induction and deployment of the full spectrum of adaptations and mutations representing ~4 billion years of speciation, yielding all current biological systems including those maintaining and repairing the genome. They can be identified and elucidated by nonselective 'panning' followed by associated analytical systems of increasing sophistication, resolution, precision, rate, and throughput (Figures 2-4) [1,2-5].

EGS and *CA RTO* are dependent on flexibility, adaptability and imprecision of ecosystems including those affecting the selection or counter-selection of mutations and adaptations (Figures 2-4), [1,2-7]. *EGS* and *CA RTO* are indispensable for the elucidation and control of relevant mechanisms of mutation by dysregulation of evolutionarily selected genes for the maintenance and repair of the genome. Despite perceptions of mutual exclusion, *EGS* and *CA*

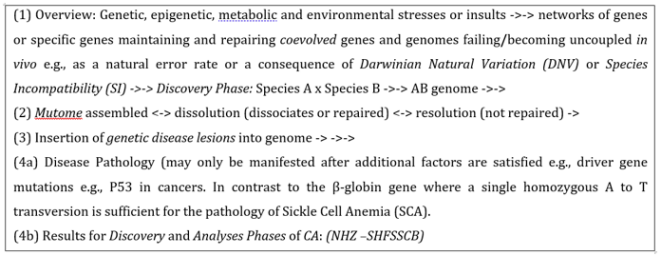

Figure 1: Schematic representation of insertion of genetic disease lesions or assembly/functions of the *Mutome* in the choice between its dissolution and resolution.

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, Computational Sciences and Mathematics (refs 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 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 its progression.

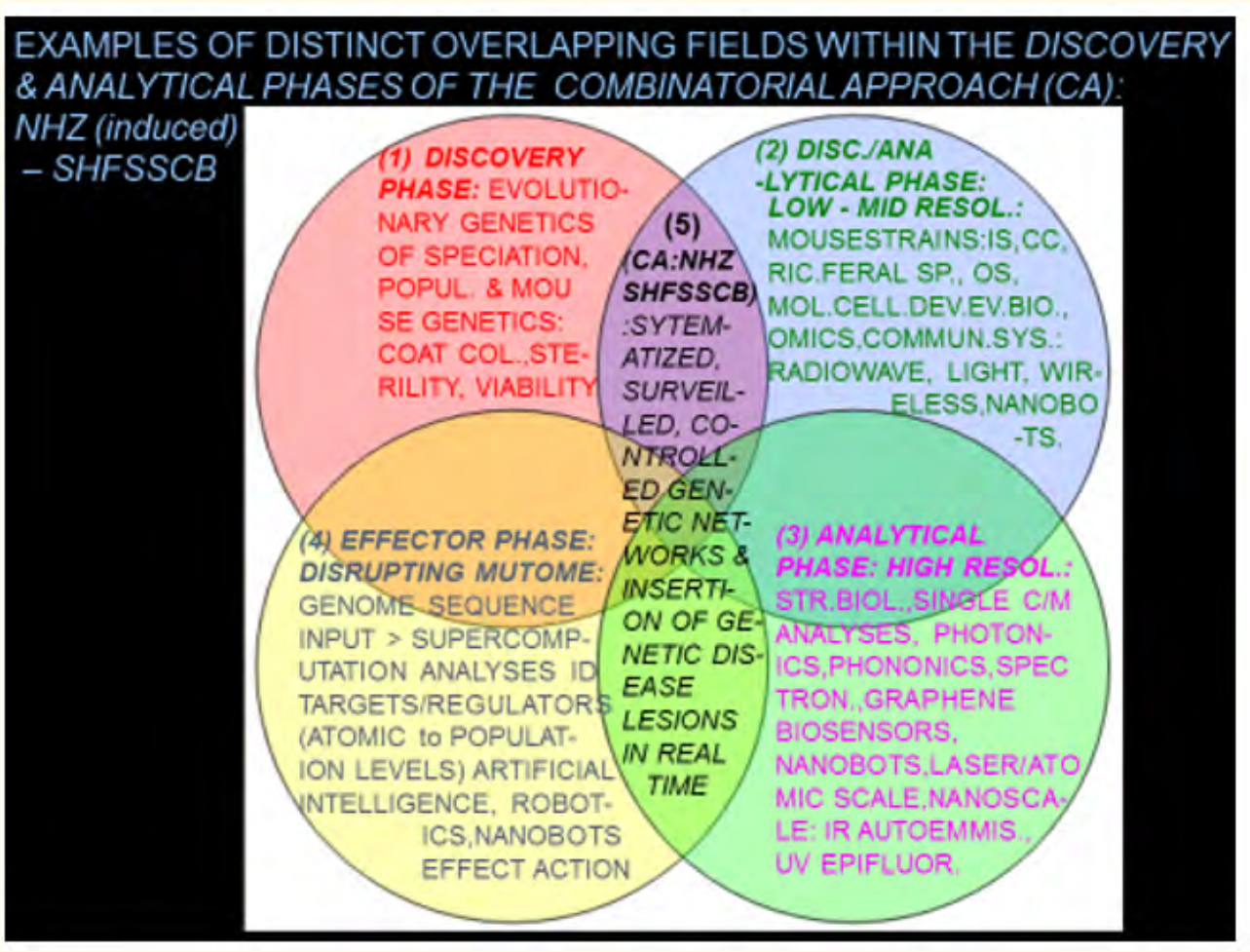

Figure 2: Potential pathways/overlaps and components of the *Combinatorial Approach (CA) – Discovery and Analytical Phases.*

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 categorising 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 wide range relevant to and are interchangeable or replaceable but designed for *Discovery* and *Analytical sciences*. The central sector (5) of overlap between all 4 independent sectors (1-4) represents the combinatorial, associative, synergistic, serendipitous, unexpected consequences in addition to natural or planned projections 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* testing. The roles or principles of *SI, Panning* analogies, assembly and other details are discussed in the text.

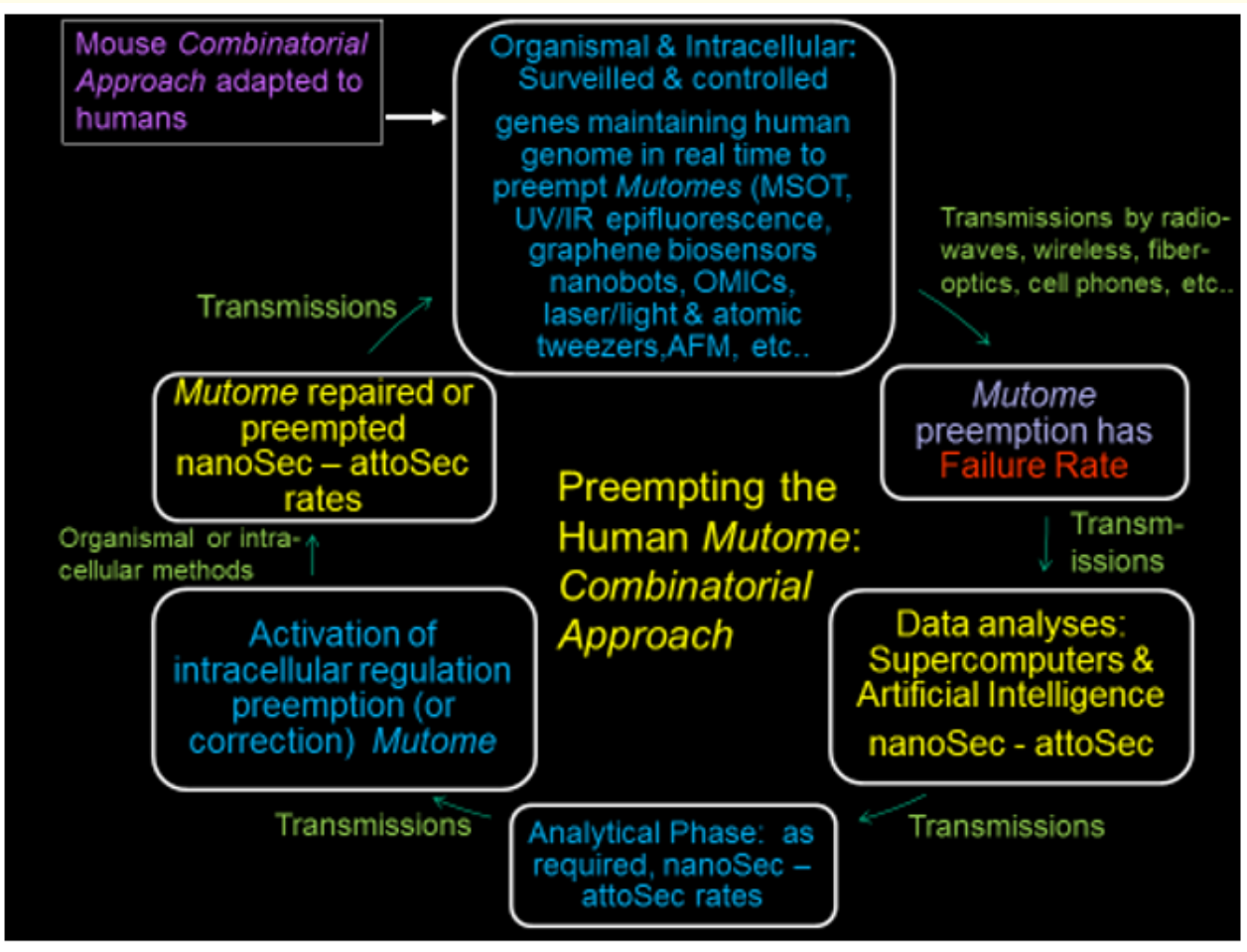

Figure 3: Potential schematic of *Real Time Operations (RTO)* of *CA* first tested in mice and then applied to healthy individuals, patients and global populations.

The above cyclical and graphical schematics are color coded and self explanatory. 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 (cells, organisms) and produces efferent output manifested as corrective actions for all dysregulation. The stages of the *CA* are followed by its translation 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 (refs 1 -30). The above graphical schematic is a preliminary proposal with limitations imposed by obvious physical and conceptual constraints. Of necessity, with it's development, the *CA* will be supplemented, enhanced, reinforced and modified by other Scientific fields which will find relevance in later stages and so take a natural place in its progression. 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 (refs 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 who have the additional expertise in these and other Scientific fields that will find relevance in later stages of the *CA RTO* (refs 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 insertions of distinct pre assembled modules into the International Space Station as it was being assembled.

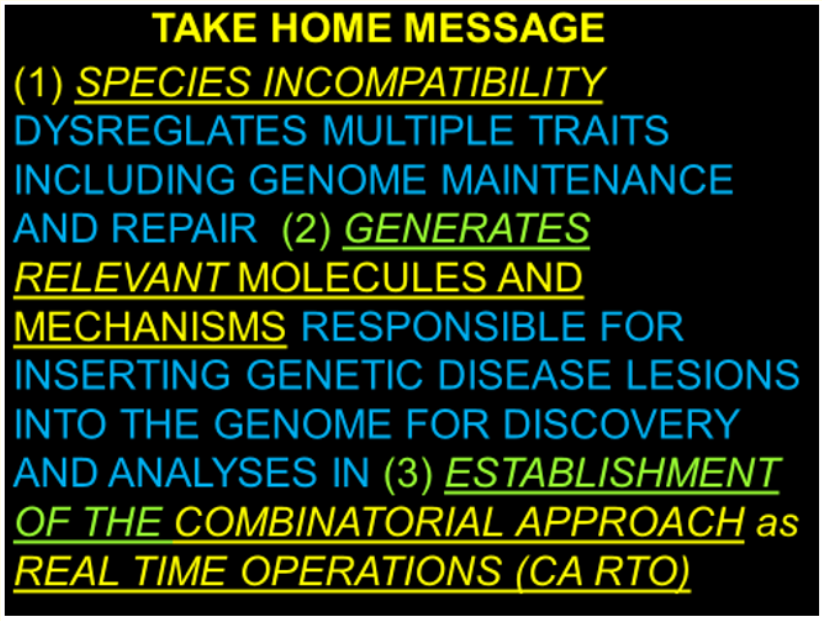

Figure 4: Summary of the basic principles of the *CA RTO* for preempting genetic disease lesions.

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 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* (refs 1 -30).

RTO are inextricably linked and interdependent, along with post-mutational therapies, on principles, and methods of contemporary medical sciences. For the simple reason that they affect biological processes, systems and developments that are spatially and temporally complementary.

The contemporary paradigm in Medicine meets immediate necessities in elucidating fundamental biological systems, as well as in therapeutic treatment of pathological conditions. However, because of their inherent scientific principles, methods, and administrative nature, they do so by perpetuating the recurrence of genetic diseases. In contrast, the *CA RTO* meets long term necessities and breaks the cycle of perpetuating the recurrence of genetic disease states. As a result of natural, planned, and serendipitous progressions and synergisms between independent scientific, technical, and societal developments, the *CA RTO* predicts an emergence of quantum or exponential progressions in healthcare. Despite the resources documented in a vast literature, all Biomedical Research either enforces work on high 'resolution-precision-throughput-focus' processes or investigations. They yield fundamental discoveries in the Life and Physical Sciences as well as in applications and management of post-mutational therapies. The consequence of this policy is the premature applications of standards of rigor and controls that are drawn from established and productive but narrow areas of research. Therefore, making them contextually irrelevant to Field conditions where *EGS* operates (Figure 2-4), [1,2-5].

The inflexibility of the scientific systems and methods of these contemporary fields precludes the harnessing of fields such as *EGS* and specifically *SI* in identifying and elucidating mechanistically relevant failures of networks of genes maintaining genomes as e.g., in approaches such as the *CA RTO*. *EGS/SI* which is an indispensable component of the *CA RTO,* is dependent on flexibility, adaptability

and imprecision of ecosystems including those affecting mutations and adaptations (Figure 2-4), [1,2-7]. *EGS* is indispensable for the elucidation of relevant mechanisms of mutation by induction of dysregulation of evolutionarily selected genes for the maintenance and repair of the genome in living organisms. A central, illustrative consequence of this contradiction remains unaddressed. Despite the power of contemporary methods, the question of the mechanistically relevant basis of insertions of genetic lesions into the genome of living organisms remains unanswered. After more than 100 years of work and the allocation of billions of dollars to its solution, in practical terms it remains unanswerable - favored models notwithstanding! As for example, in the A to T transversion in the β-globin gene causing sickle cell anemia (Figure 2-4), [1,2-7].

Our working model for mechanistically relevant insertions of genetic lesions is represented by all its known or putative components in various states of equilibria from initiation to insertion, known as the *Mutome* (Figure 2-4), [1,2-5]. Despite the availability of scientific principles and technologies of sufficient scale, precision, resolution or rate and sophistication, the current and primary barrier to preempting of a genetic lesion stands unresolved. This is principally due to the absence of a harnessed source of mechanistically and contextually, relevant, and representative aberrations or intermediate aberrant products of evolutionarily selected genes, proteins, networks, and systems for the maintenance and repair of genomes. Those which can be induced to insert these lesions for subsequent elucidation and control of relevant networks. Therefore, acquiring the ability to induce relevant pathways for preempting such genetic lesions. However, all these barriers can be surmounted, so the *Mutome* becomes mechanistically elucidated by deploying a combination of scientific principles and methods.

HI and *SI* are manifested in *Interspecific (IS) genomes (ISG)* or *Interspecific Organisms (ISO)* and subsequently applied to elucidating the *Mutome* by the resolving power of contemporary methods. *SI* and *ISO* generated, and mechanistically relevant biological dysfunctions can occur within single generations and across evolutionary radiation from microbes to Hominins (Figure 2-4), [1,2-7]. The *CA RTO* emerging from this elucidation, would be an automated system for the preemption of genetic disease lesions that for illustrative purposes, has operational similarities with to the brain. Namely, in its continuous, simultaneous, autonomous, coordinated, molecular and neurophysiological functions down to levels of a single neuron or synapse.

An essential and foreseeable component of *CA RTO* is whole genome scanning (WGS) per cell and simultaneous communication of the collected input data for computational analyses. This communication could be based on electromagnetic/photonic or gravitational (B2C, C2B, B2B) or their hybrid systems and would represent input data for banks of Supercomputers or when applicable for Quantum Computers. With the simultaneous processing and redirection of computational output to genomes for effecting preemption or repair of a genetic lesions. It is effected by inducing networks of genes and proteins previously identified with algorithms or emerging from *EGS/SI* and *CA RTO*. The actual computational output being communicated to genomes by redirected versions of the same communications systems delivering input to computers. Super/Quantum Computers can be programmed with *Artificial Intelligence (AI)* and a spectrum of algorithms for recognizing and correcting genetic lesions identified by *SI and ISO* . They would be pre-assembled resolution(s) of the *Mutome* in *CA RTO.* This is akin to the collection and processing of high resolution, high-density and high-volume data from the analyses of extreme dimensions of Deep Space or Subatomic particles (Figure 2-4), [1,2-7].

Some simple estimations of mutation frequencies based on accepted minimal values of biological components are informative for the purpose of healthcare policies. The *Minimal Cumulative Mutation Exposure per Person per Lifetime (MCMEPPPL)* is calculated as $8.042695817 \times 10^{34}$ (1), calculations in full length version of this manuscript are in preparation). The *MCMEPPPL* is represented by permanent mutations as well as by transient mutations present in fractals of space and time per person before they are eliminated from the gene or coding sequence fraction of the genome. The *MCMEPPPL* could be significantly magnified by the inclusion of multiple known factors. These include those at the genic level (maximal frequency per gene), whole genome level including known unstable sequences (>98.5%), maximal numbers of rounds of cell division and DNA replication, not restricted to whole body total cell replacement (e.g. erythrocytes and their progenitor stem cells; intestinal and skin epithelia), total global human population ($\sim 8 \times 10^{9}$), and maximal gender, ethnicity, geographical and other factorial dependencies of life expectances.

The *MCMEPPPL* could also potentially be magnified by the inclusion of multiple unknown factors. These could be contributed by aberrant interactions at the sub-atomic (Darwinian as per Physicists), atomic, molecular, organellar, cellular, inter-tissue, inter–organ, metabolic, organismal, populational, microbiota, inter-and intra-species, ecosystems, environmental and Outer Space factors. Although the proportion of the *MCMEPPPL* that contributes to the minimum of 65% of all diseases having a genetic component, and at an expanding frequency is not known, it is clear that benign neglect of the *Mutome* is an abdication of responsibility [1,2-7].

All elements of the *CA RTO* have had some work done on them but require integration, synthesis and elevated organization, sophistication, and processing. Although the *CA RTO* faces daunting conceptual, scientific, technical, economic and ethical challenges, they are all surmountable. The exception being the insurmountable scientific barrier emerging from a lack of familiarity with the only source of relevant mechanisms for inserting genetic lesions – *EGS* and *SI.* Work on the *CA RTO* faces the same challenges as those faced by other undertakings in civilization that are of equivalent scale and complexity. Paradoxically none could have access to greater resources, scientific principles, methods, published and unpublished data. The current benign neglect of *MCMEPPL* exposure classified as spontaneous mutations, and the *CA RTO* arise from a multitude of unsupported rationales. All of which reinforce post-mutational therapies such as Precision or Translational Medicine, Gene Therapy, or therapeutic intervention at the level of management of immediate pathological consequences of genetic disease lesions. They contribute to the increasing frequency, type, and impact of genetic diseases. Including the incurring of dehumanization and healthcare costs of intractable diseases and hundreds of trillions of dollars per annum [1,2-7]. The *EGS* principle of *Species Incompatibility* on which the *CA RTO* for preempting genetic disease lesions is founded, has been recognized for over 150 years. Yet the *CA RTO* has only been recently advocated and initiated by our work which necessitated the founding of the nonprofit *LSINJ* and the independence of its advocacy [1,2-7].

Practical or operational consideration for the above consequences are the pre-requisites for the initiation as well as direction of *CA RTO*. They are indispensably dependent on advocacy and advocates developed by long term exposure, experience, integration, and synthesis of multiple fields of science [1,2-7]. As well as long term resilience in contending with systematic challenges of uninformed Detractors by drawing on the lessons in convictions taken from those at the pinnacle of science, history, and civilization. Including the likes of Albert Einstein, J. Robert Oppenheimer, Andrei Sakharov, Barbara McClintock and Richard Feynman [2-5]. Lessons that are indispensable for resisting insular and counterproductive sociopolitical forces contradicting the most fundamental definitions of science and the Public Interest. As has been driven home by our experience over the last 40 years of research, the initiation, and the direction of the *CA RTO* and the *LSINJ* as an undertaking are often mutually exclusive with restricted traditional trajectories in Science, Medicine, Academia, Pharmaceutical and Biotechnological enterprises. Necessitating the protection and independence of the nonprofit foundation *LSINJ* and its advocacy for the *CA RTO* [2-5]. Yet remaining open to eventual and indispensable collaborations, following the abatement of attempts by vested interests to repurpose the *LSINJ* into undertakings that are scientifically highly redundant and legally noncompliant with its nonprofit status. All of which could be harnessed for the Public Interest or the Common Good, should negotiated understandings of, seemingly divergent and yet complementary interests, in healthcare escape from reflexive exclusion to become a reality. These negotiations would represent immediate therapeutic necessities for patients as well as those that are long-term necessities of populations, policy, and human costs.

The nature of the *CA RTO* can have profound implications that extend far beyond its role as an instrument for eventually releasing Humankind from the consequences of passive perpetuation of recurrent genetic disease lesions. These are represented by its potential impact on progressions or regressions of Evolution and Speciation which necessitate considerations on a Societal scale [2-7]. There are parallels in History on interdependent processes with opposite existential consequences for Humankind and the current policy discussions. Namely the enforcement of the contemporary Paradigm in Medicine to the exclusion of the *CA RTO*. [1-5].

The vectors, dynamics, and parameters of the ongoing conflict between the *LSINJ* and the greater scientific community

in initiating the *CA RTO* has several precedents in history. Most notably they are similar to policy decisions with opposite and existential consequences that were made during the Second World War (WWII) and the subsequent Cold War [2-5]. Scientific and policy decisions that either delayed, if not entirely averting, incineration of the planet by nuclear weapons or in contrast sociopolitical considerations subsuming scientific decisions that resulted in famines with the loss of life on a calamitous scale [2-5]. Yet (WWII) and the Cold War also produced inspirational examples of upholding the 'Greater Good' by citizens of the principal adversaries. These were striking examples of the Human Spirit in overcoming one of the Darkest Chapters of History - both on and off the battlefields of (WWII) [2-5]. The LSINJ is subject to a microcosm of these forces and dimensions. This historical narrative serves as a beacon for its position in upholding the Public Interest or Common Good intrinsically represented in the CA RTO.

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