TETRAD Institute of Complex System Dynamics

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Population Health Equity Bioinformatics Resource (PHEBR) is a key tool for developing understanding of neurophysiological turbulence and entanglement leading to dysautonomic, autoimmune, arrhythmic pathologies and also pleasure/pain dysfunctions

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This memo addresses things that pertain to the Neuroplex-C project and other aspects of TBD, TND, PSD research which involve TETRAD Institute and several collaborators in academic, medical, and corporate centers of research and clinical practices. At the close of this memo are URLs to supplementary materials that are presently available for access.

[1]
Prefatory remarks regarding PHEBR:

> <u>PHEBR = a population-wide bioinformatics data resource providing detailed (anonymized) information on health histories including both quantitative and qualitative information</u>.

This resource must include:
- diagnostic history data of several types (e.g., EKG, echocardiography, and pertinent other imaging and recording, as well as histories of hypertension, temperature flux and arrhythmia, equilibrium and balance episodes, and other quantitative and qualitative parameters over life-history, as much as possible)
- patient and family behavioral and lifestyle data (both specific, as known and accessible, and through computational inferences) such as nutrition, exercise and fitness, exposure to and ingestion of toxins and stressors of chemical nature (e.g., air, water, food) and particularly psychological and social stress (e.g., abuse, anxiety, depression, trauma, PTSD).

Research and clinical studies, globally, provide the rock-solid basis for the assertion that what are termed neuroelectrochemical stressors – within the range of sources indicated above – are a major contributing factor – even beyond genetic factors – leading to subsequent disorders and diseases of the types indicated above. These pathologies commence particularly in adolescence and middle age and the outcomes are almost universally of only two types:
- extraordinary complications, disabilities and comorbidities, reducing the potentials for a normal lifestyle (including employment and a professional life) and for an average-length lifespan
- early and often sudden death

[2]
Building the PHE Bioinformatics Resource (PHEBR)
This can be accomplished through the following steps and phases. TETRAD Institute ("TETRAD") in conjunction with one or more principal medical centers (universities and/or hospitals, as described further below) will establish the primary system: model, architecture, computational and analytical components, and methods for acquisition and dissemination of data content to users (research and clinical).

The database(s) and the synthetic ("AI") intelligence components are straightforward, non-complex, and principally based upon existing, proven, accepted technologies. There are collaborative partners at other institutions worldwide in all aspects of PHEBR implementation and use (as summarized below).

[2.1]
The focus of the PHEBR begins with large-scale population health data acquisition (as indicated above) and analysis capabilities. Along with the capabilities mentioned above, there are two critical components of data acquisition that are viewed within the research/clinical community as major positives:
- incidents and probabilities of epidemic or pandemic type diseases (e.g., influenza and COVID-type viral infections; e.g., Long-COVID), with a focus upon early detection of infection cases, attention to variants, and prediction of transmission & distribution through the general population

- pregnancy and first months after childbirth – these are significant risk-periods for certain demographic segments of the female population, and minority groups in particular.

[2.2]
The PHEBR will include computational (modeling, simulation, and dissemination) capabilities for:
- analysis of deficits and development of methods (mechanisms, procedures) for removing deficits in diagnostics and early detection of disorders and diseases:
  - cardiovascular and dysautonomic disorders as the primary focus
  - autoimmune diseases including multiple sclerosis (MS), Alzheimer's, Parkinson's, Lupus, which are particularly challenging to detect, particularly in early-onset or pre-onset stages, in general, among any and all populations, and for which many minority populations are receiving inadequate diagnostic and preventive medical care including education as well as prophylactic/therapeutic treatments.

- analysis of deficits and development of methods for improving day-to-day and long-term care of patients afflicted with such disorders (i.e., removing deficits in long-term care of persons with physical and mental disabilities that prevent or reduce dramatically the person's ability for self-mobility (e.g., walking), self-care (e.g., household, personal), and social interactions).

Within the PHEBR there is extensive employment of synthetic intelligence ("SI", aka "AI") algorithms, and the primary applications are in:
- decisions regarding authenticity and usability of data elements
- inferences where data is incomplete, sketchy, and unambiguous
- natural language understanding for data originating as text descriptions
- inferences regarding sources for new data on patients and patient group types that should be obtained
- inferences including forecasts for symptoms and specific pathologies to be targets of examination and diagnostics including by empirical, instrumental forms of measurement and evaluation

The central component of the SI technology used within the PHEBR is known as Seldon. This is a composite of pattern recognition, inference and predictive software developed over a period of years by members of the TETRAD collaborative research team. Seldon has been designed for large datasets with high degrees of uncertain, incomplete and conflicting data.

[2.3]
The PHEBR includes data pertinent to the following (which constitute the focus of a current, long-term, multi-institutional, international consortium in which M J Dudziak and TETRAD are involved, serving as principal investigator and institution ("Neuroplex-C"):

- Cardiomyopathies[1] including but not limited to progressed development of arrhythmias such as tachycardia and AFIB
- Myocarditis and percarditis, and consequent cardiomuscular disorders linked with infectious diseases and/or other forms of inflammatory disease, including but not limited to COVID-19
- POTS (postural orthostatic tachycardia syndrome)
- MALS (median arcurate ligament syndrome)
- EDS and hyperelasticity within the arterial network and particularly the aorta
- Hypertension, atherosclerosis and myocardial infarction
- Gastrointestinal disorders (such as IBS, POI and Crohn's) linked with the above, particularly POTS
- Dysautonomic disorders which are viewed as being related in causal and/or concomitant relations

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1   Dilated (DCM), hypertrophic (HCM), restrictive (RCM and left-ventricular non-compaction (LVNC), with particular attention to the other conditions, disorders and diseases referenced above in this proposal context

with one or more of the cardiac dysfunctions listed above
- Psychological disorders linked with several of the above conditions, particularly PTSD and depression)
- Special attention to disorders with both neurophysiological components that are associated with the following areas of investigation:
  - chronic pain
  - post-surgical trauma including development of adhesions affecting cardiovascular, gastrointestinal and urological organs
  - psychological reactions including development of dependencies upon addictive substances

[2.4]
The PHEBR meets clear and consensus-agreed needs expressed within the medical communities focused upon these categories of disorder and disease. PHEBR provides new, systematic, thorough, and large-scale bioinformatics and supports the subsequent development of useful large-population medical databases, covering precisely the disorder and disease topics listed above. PHEBR can be used within academic, public-sector, and corporate (e.g., pharmaceutical industry) sectors for:

- healthcare planning by all types of provider professionals and institutions
- pharmaceutical design and development
- medical device design and development
- pregnancy and postpartum healthcare
- long-term healthcare
- social services for the disabled
- public health education for the general population, especially youth

[3]
Partners in building the PHEBR and in its dissemination, use and future contracts
Expected, proposed, and in-discussion partner individuals and institutions include some of these already invloved with MJD and TETRAD in the Neuroplex-C project (referenced below, with bibliographic references).

Note that in most cases, there may be zero funding requirements, or a very modest consulting arrangement, for most of these institutions and their involvement, because of other ongoing support mechanisms already in place or confirmed otherwise.

§ Among USA persons/institutions:

Johns Hopkins University	New York Univ.
Columbia Univ.	Vanderbilt Univ.
Cleveland Clinic	Mayo Clinic
Texas Heart Institute	Meharry Medical College
Michigan Technological Univ.	Dysautonomia International

and several private healthcare and pharmaceutical corporations

§ Among non-USA persons/institutions:

Norwegian Univ. of Science and Technology	Karolinska Institute (SE)
Oslo Univ. (NO)	Stavanger Univ. (NO)

Uppsala Univ. (SE)   Göttingen Univ. (DE)
Max Planck Institute for Dynamics and Self-Organization (DE)
German Center for Cardiovascular Research (DE)
and several private healthcare and pharmaceutical corporations

[4]
The PHEBR grows out of research in autoimmune disorders with focus upon neuro-electrochemical stressors ("ANCES") and in the complex of neurological and cardiological investigations that comprise the Neuroplex-C Project. Additional information resources can be found at:

www.neuroplex-c.tdyn.org

The ANCES theoretical framework provides one particular area of PHEBR application that holds promise for providing a deeper understanding of the etiology and metabolism of several conditions and disorders that are often relegated to the category of "syndrome" and also not viewed as having pathologically supportive relationships among each other. While this research direction is by no means the primary near-term motivation for PHEBR, given other conditions and diseases as previously indicated, the value for exploratory investigations is high considering the potential beneficial outcomes for both theory and clinical practice.

The following key points summarize Autonomic Neurophysiological Control and Electromolecular Stress (ANCES) (and the role of chronic exposure to and metabolism involving a large class of neuro-electrochemical stressors) and provide a view into new research that can bear substantial benefits for a very large segment of the human population.

◇ Ganglial turbulence and noise (basal ganglia and peripheral nervous system (PNS) ganglia)
◇ Signal conflict and neuronal constructive/destructive interference wave patterns
◇ Growth-formation of ganglia tangles and knots
→ → → ◇ observed dysautonomic and arrhythmic reactions
     → → → ◇ repetitive and episodic disorders leading into chronic pathologically stable disease
          → → → ◇ inflammatory response as a chronic condition leading to autoimmune reactions
             and reduction in immune system strength for resistance to external pathogens
             (and other general inflammatory consequences)

[4.1]
Among dysfunctional conditions that this model has direct bearing are some that are not commonly associated with the systemic pathologies described above, including those of a cardiovascular and gastrointestinal nature. We believe that the ANCES theoretical framework, with the type and character of the data that comes from a PHEBR databank, will help to open up new understanding of the dynamics within the psychophysiology of pleasure and pain mechanisms involved in a wide number of dysfunctions for individuals and interpersonal relationships, including:
- libido, sexual arousal and dysfunction, - both male and female
- pleasure and pain responsiveness including addictive and abusive behavior
- substance abuse and addiction, particularly involving alcohol, tobacco, opiates and related drugs in widespread use

The PHEBR has sufficient mandated value without considering the long-term and far-reaching research potentials described. It is a necessary healthcare resource for many widespread "common" disorders and

diseases, but it also provides windows into behavioral and lifestyle contributors to stressors at the molecular and macroscopic and psychological/systemic levels which can have dramatic positive impact on our understanding of the origins, the metabolics, and the therapeutics that pertain to many serious conditions affecting the whole of society.

[4.2]
Summary of possible consequences of chronic traumatizing turbulence within the CNS and ANS that may be attributed to neuro-electrochemical stressor agents

[typical trigger period]	[conditions]
[early infancy, < 1 year]	SIDS
[adolescence/young adult]	MS, Lupus, CFS, cardiac arrhythmia, POTS
[middle/later adult]	sexual dysfunctions, IBS, Chrone's, other cardiac arrhythmia
[older adult]	(triggering/exacerbating) Alzheimer's, Parkinson's, AFIB, atherosclerosis

[5]
Additional background information including references, bibliographies, and matters of contractual and other formal natures, is available. The next step is to begin meetings and discussions, commencing via teleconference and then is appropriate, in person, with the potential for seminars and lectures.

[6]
The PHEBR is the most strategically intelligent and socially proactive method to accomplish many of the long-term objectives of several groups of interest within medicine and public health, beginning with the needs, clearly identified and strongly, if not universally, agreed upon, for addressing health inequalities and inequities among many diverse and minority groups of the human family. In addition, the PHEBR opens up for the first time in history the possibilities of linking behaviors, habits, and lifestyle factors that are generally missing from the clinical "diagnostics-to-therapeutics equation", with a significant number of medical conditions that have historically been poorly understood, often misdiagnosed or simply ignored and deemed "psychological", but which are most clearly linked with systemic degradation that damages individual and family life, social structure, and often leads to early death. I and TETRAD are prepared to take the initiative to make the PHEBR a reality and to put it properly into the hands of all healthcare practitioners.

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