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Towards personalized medicine in maternal and child health: integrating biologic and social determinants

David K. Stevenson[1], **Ronald J. Wong**[1], **Nima Aghaeepour**[2], **Ivana Maric**[1], **Martin S. Angst**[2], **Kevin Contrepois**[3], **Gary L. Darmstadt**[1], **Maurice L. Druzin**[4], **Michael L. Eisenberg**[4,5], **Brice Gaudilliere**[2], **Ronald S. Gibbs**[4], **Ian H. Gotlib**[6], **Jeffrey B. Gould**[1], **Henry C. Lee**[1], **Xuefeng B. Ling**[7,8], **Jonathan A. Mayo**[1], **Mira N. Moufarrej**[9], **Cecele C. Quaintance**[1], **Stephen R. Quake**[9], **David A. Relman**[10,11], **Marina Sirota**[12,13], **Michael P. Snyder**[3], **Karl G. Sylvester**[7], **Shiying Hao**[8,14], **Paul H. Wise**[1], **Gary M. Shaw**[1], **Michael Katz**[1]

[1]Department of Pediatrics, Stanford University School of Medicine, Stanford, CA 94305, USA

[2]Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA

[3]Stanford Center for Genomics and Personalized Medicine, Department of Genetics, Stanford University School of Medicine, Stanford, CA 94305, USA

[4]Department of Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, CA 94305, USA

[5]Department of Urology, Stanford University School of Medicine, Stanford, CA 94305, USA

[6]Department of Psychology, Stanford University School of Humanities and Science, Stanford, CA 94305, USA

[7]Department of Surgery, Stanford University School of Medicine, Stanford, CA 94305, USA

[8]Clinical and Translational Research Program, Betty Irene Moore Children's Heart Center, Lucile Packard Children's Hospital, Palo Alto, CA 94306, USA

[9]Departments of Bioengineering and Applied Physics, Stanford University, and Chan Zuckerberg Biohub, Stanford, CA 94305, USA

[10]Department of Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA

[11]Infectious Diseases Section, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA 94306, USA

[12]Bakar Computational Health Sciences Institute, University of California, San Francisco, San Francisco, CA, USA

Correspondence: Ronald J. Wong (rjwong@stanford.edu).

AUTHOR CONTRIBUTIONS

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[13]Department of Pediatrics, University of California, San Francisco, San Francisco, CA, USA

[14]Department of Cardiothoracic Surgery, Stanford University School of Medicine, Stanford, CA 94305, USA

A person's health is dependent upon the interaction of one's biologic attributes with one's social and physical environments. The purpose of this commentary is to provide our collective opinion about how integration of biologic and social determinants of health in pregnancy can lead to "personalized" care and improved outcomes for the mother and her baby. We have based our opinion on our experience with a transdisciplinary research effort to predict and consequently, prevent preterm birth (PTB).[1] Our fundamental concept is that the disposition of a pregnant woman should be viewed simultaneously from multiple perspectives. What is seen depends upon the specific observational tools themselves as well as upon the various measures that result from their applications. While this usually reflects the conceptual framework and the expertise of different observers, it also can skew the effort towards a single perspective. Traditionally, medicine has been divided into disciplines, reflecting several perspectives—a situation that is also true of the sciences. With respect to pregnancy health, personalized medicine offers a promise of designing preventions and therapies that take advantage of the integration of a variety of observations, not just exclusively of only one, that relate to a particular pregnancy. This offers a "personalized" means of understanding the health disposition and life trajectory of any individual pregnant woman and her offspring. In contrast, observers, who focus solely on any singular domain, may fail to capture fully this complex relationship.

Current clinical approaches to the prevention of PTB include risk assessment such as by detecting a short cervix by ultrasonography[2] and interventions such as 17-OH progesterone,[3] and low-dose aspirin,[4] but these have been met with limited success in preventing PTB overall. For example, in a recent trial of low-dose aspirin given to nulliparous women with a singleton pregnancy, the intervention reduced PTB before 37 weeks of gestation significantly, but only from 13.1 to 11.6% (relative risk (RR): 0.89; 95% confidence interval (CI): 0.81, 0.98); $p = 0.012$). Clinical interventions are limited because we do not completely understand the complex pathogenesis of PTB and because we are unable to predict which women will respond to a specific intervention. The limited benefits of current clinical care therefore call out for a more personalized approach.

Studying PTB (delivery before 37 weeks' completed gestation) can be used as an example for the potential of integrating many of these observational domains[5] since it is a complex human condition.[6,7] Such a model would allow the prediction of disease occurrence and guide effective, preventive and therapeutic interventions. To a greater extent, it would also offer a more comprehensive understanding of the complex causes of health disparities of women[8] and offspring that have roots both in their ancestry[9,10] and in their current social and/or physical environments.[8,11]

We propose that no disease should be categorized solely in terms of biologic or social determinants if we are to gain a full understanding of its etiology, even when the concept of social determinants includes a set of broad environmental factors. Understanding the

complex interrelationship between biologic and social factors may be facilitated by complex mathematical algorithms. The application of innovative computational techniques is revolutionizing the practice of medicine, but is also exposing the arbitrary limitations of relying just on a single disciplinary approach.[12] In fact, personalized medicine requires such a systems-based approach to the understanding of maternal and child health. In this commentary, we present a perspective on personalized medicine in maternal and child health through the lens of a transdisciplinary research enterprise to predict and prevent PTB—an example of an effort to personalize decision-making in pregnancy through integrating various domains of risk factors represented by biologic and sociologic determinants.

SOLVING THE PUZZLE OF PTB

PTB is now the primary worldwide cause of death in children under 5 years of age—more than 1 million deaths annually[13]—and in about half the cases, this “calendar” event is spontaneous and enigmatic.[14] Understanding how the immunologic tolerance of a pregnant woman to her fetus is initiated, maintained, and sometimes disrupted might provide clues to understanding not only normal parturition and PTB, but probably also certain cancers, autoimmune diseases, and a variety of other “proinflammatory” conditions, such as cardiovascular disease or even aging itself.[15] Thus, PTB is not simply a calendar event, it is an immunologic anomaly[16]—a syndrome with multiple etiologies characterized by mutual loss of tolerance between the mother and fetus.[6,7] Many mechanisms have been proposed to explain spontaneous preterm labor, each of which likely has numerous biologic and social determinants.[8,11]

Ironically, even normal parturition is not fully understood with respect to what triggers its initiation.[6,7] Nonetheless, labor (both term and preterm) is characterized by increased myometrial contractility, cervical ripening, rupture of the chorioamniotic membranes, and ultimately expulsion of the fetus. Collectively, these events have been referred to as the common pathway of parturition. Many pro-labor initiating factors, such as chorioamnionitis, a short cervix, maternal stressors, placental senescence, among many others, can contribute to inflammatory signaling with increases in cytokines, chemokines, and prostaglandins, preceding these physical changes and resulting in PTB.[17] Throughout pregnancy, progestational signals, such as increased progesterone levels and increased progesterone responsiveness, contribute to a “progesterone block” of any prelude of inflammatory signaling, the expression of progestation genes, and consequent uterine relaxation and quiescence throughout gestation—until mysteriously just the right time (term) when labor ensues.[18] However, in human pregnancy, it is important to note that the loss of the “progesterone block” is not just a consequence of a drop in progesterone levels. Indeed, it must also involve a change in responsiveness to the hormone through mechanisms that still need to be elucidated.

Progress is being made in understanding the biologic cascades that coordinate parturition at term or before term, which, in fact, may not be the same. However, this does not diminish the importance of many other factors (upstream and/or downstream (etiologically)), such as socioeconomic inequalities, racial disparities, nutritional intake, food security, access to care, environmental exposures, etc., that can affect this biology. Interventions may be

undertaken that address specific biologic cascades directly or via many of these other "nonbiologic" factors, which can engage the biologic machinery in ways that have yet to be elucidated. Knowing not only how and when to intervene, but when to let nature take its course, are difficult questions when practicing personalized medicine. We propose that the answers to these questions require the integration of data from many disparate lines of investigation, with scaling-up of whatever screening measures and new interventions (targeting at genetic and/or cellular levels) that might be revealed to the community and population levels.

Most importantly, understanding a fundamentally complex human condition like pregnancy, and elucidating a pathologic pregnancy outcome like PTB, will require a novel conceptualization of the "personalization" of medicine, which will include more than precision technologies and a better understanding of the biologic cascades leading to the initiation of labor and how to target therapies safely. It is important to realize that this concept will require an expanded notion of "personalization," including an appreciation that factors external to the person, i.e., their community and society at large, which can contribute to their personalized risk profile through numerous contextual aspects, such as those associated with policies, safety, care, and physical environments.

CONVERGENCE SCIENCE OR TRANSDISCIPLINARY RESEARCH AS AN INVESTIGATIVE APPROACH TO A COMPLEX HUMAN HEALTH PROBLEM

Because PTB is a complex problem (like many other maternal and child health issues), simply identifying risk factors, most of which historically have been demographic, psychosocial, or environmental in nature (broadly social determinants), is not sufficient to reduce its occurrence or eliminate it as a problem. However, a continued examination of novel risk factors still remains important. As the "big data" revolution has increased the availability of (information) surrounding pregnancies and births, our group and others have explored modifiable factors, such as exposures to maternal medications or pesticides, etc. as well as paternal contributions (e.g. health, demographics, medications) on the health of the mother, pregnancy, and child.[19–27] Nonetheless, it is still important to identify the underlying biomarkers associated with various social determinants, in particular proteins, metabolites, and other molecules in the circulation or even at the tissue level. Moreover, assessing the disposition of a pregnant woman in terms of biomarkers may be necessary, but not sufficient, to understand her risk for PTB, even though some measures, for example, metabolites, are most proximate to the biologic phenotypes of interest to the physician. We require information about the genes themselves, and more importantly, their transcripts, reflecting how genes are being expressed, and ultimately individual cell-specific signaling behavior. These sources of data are essential to the task. Thus, for our purpose, a collaborative group of scientists from a variety of disciplines relegated into teams and focused on solving the problem of PTB has provided opportunities for discovery, asking fundamental questions from a variety of perspectives and inventing new tools for our various investigative efforts.[1,28]

Our goal has been to assemble an integrated maternal profile of demographic, psychosocial, exposomic (environmental), microbiomic,[29,30] genomic, transcriptomic (cell-free (cf)-RNA),[31,32] proteomic, metabolomic, and single-cell immunologic data that reflects a PTB signature (Fig. 1).[5] Metagenomic and functional analyses of the microbiomic data have contributed to an additional sophistication in our attempt to understand the "immunologic anomaly" of PTB.[33] Ultimately, we aim to create a fully integrated personal "omics" profile of normal and pathologic pregnancies.[5] One of the first questions we asked was: "Is it possible to monitor noninvasively the developmental gene expression program of a human fetus?" We now know that the answer is "yes". Most people are now familiar with the utility of cell-free nucleic acids in the diagnosis of aneuploidy, just by measuring fetal cf-DNA in the circulation of the mother.[34] However, there is also cf-RNA from the mother, fetus, and placenta in the circulation, and simply sampling a woman's blood throughout gestation can allow a kind of "eavesdropping" on a biologic conversation between the mother, the fetus, and the placenta, revealing not only what genes are present, but also what genes are being expressed and at what levels at different points in gestation.[31] It is even possible in some instances to identify the source of the cf-RNA.[32,35]

Such gene expression patterns might provide insight into the maintenance of tolerance for the fetus in a normal term pregnancy, and also into identifying those changes in immune cell signaling that might be associated with local tissue changes that trigger the initiation of preterm labor. In fact, we have identified genes that display temporal changes across gestation.[31] Some of these genes are expressed early, some are upregulated, and some are downregulated over the course of pregnancy, suggesting the presence of a "transcriptomic clock" that characterizes normal pregnancy, and can also be used as a reference to identify changes in gene expression associated with PTB.[31] Many of these temporal changes occur in the expression of immune genes. Indeed, the expression of some genes early in gestation has been associated with later PTB, providing an accurate and affordable, noninvasive diagnostic test for estimating gestational age (GA) (nine genes) or potentially the risk of spontaneous preterm delivery (seven genes).[31]

It is remarkable that this model for estimating GA approximates the accuracy of ultrasonographic estimation of this same measure, and can predict spontaneous PTB as early as 2 months prior to the onset of the actual physical event. Thus, a noninvasive blood test for fetal development can be used to estimate GA and predict preterm delivery,[31] although it needs to be validated by largescale testing before its clinical application can be undertaken with confidence. Complementing these findings, we have also characterized an immune clock of pregnancy.[36] During gestation, there is a shift in the mother from a state of tolerance and immunosuppression to one of rejection and inflammation (parturition), with different kinds of cells (and their signaling behavior) changing over time,[37] suggesting that the immune balance of pregnancy is nature's measurement of time during gestation. Using cytometry by "time-of-flight" mass spectrometry,[38–40] we have been able to survey with unprecedented single-cell resolution simultaneously quantifying over 37 phenotypic and functional proteomic markers per cell for the analysis of pregnancy-induced alterations in immune cell distribution and signaling responses across the entire immune system.[36] This has allowed us to characterize the timing of systemic immunologic events in normal and pathologic pregnancies, as well as to identify signaling pathways. One such pathway MyD88

is exacerbated in women with a history of PTB, suggesting a sensitivity to stimuli that might account for the epidemiologic observation of increased risk of PTB in a woman with a history of PTB.[40]

Combining these results with previous noteworthy preclinical studies has set the stage for molecular targeting of the innate immune system using an allosteric IL-1R antagonist to prevent PTB while preserving defensive immunity.[41,42] A similar approach has also identified altered systemic immune cell signaling, which can predict the occurrence of preeclampsia before the onset of any of the classical signs.[43] Again, this sets the stage for targeted immune therapies to modulate the differentiation of T-regulatory cells affecting continued tolerance that was waning in a pregnancy destined for subsequent preeclampsia. Such an approach is amenable to test dimension reduction for a scalable (six-color) diagnostic assay, stratification and immune monitoring of “at-risk” individuals with the potential for an immune-modulating therapeutic intervention (e.g., low-dose IL-2), as has been proposed for treating some autoimmune diseases.[44,45]

Our main task, however, has been to integrate mechanistic immunological knowledge into a machine learning pipeline that can increase clinical predictive power.[5] Many different kinds of data from a variety of inquiries and different manners of interrogation of the same women around the same time allows this potentially very powerful approach to revolutionize the way in which we “personalize” care. Such an approach may allow the translation of one measure obtained from one way of observing into another measure from an entirely different manner of interrogation. In this way, various silos of a science can be merged for the purpose of addressing a complex human problem with more accurate diagnostics, increased prediction, and successful prevention.

ANALYTIC APPROACHES FOR THE INTEGRATION OF BIOLOGIC AND SOCIAL DETERMINANTS

Existing individual- and population-level factors identified in previous studies have not produced accurate predictive models of PTB.[46] These studies have repeatedly demonstrated that models that work well for one population do not generalize to others.[29] Therefore, the need to integrate social determinants with directly measured biological modalities is clear.

Several studies have already used combinations of biological and population-level factors to predict adverse pregnancy outcomes.[47–50] However, with increased access to patient databases and the rapid growth in the number of biological modalities measured in multiomics studies, simply merging these datasets and using a single multivariate model on the entire dataset is no longer sufficient.[5] There are several analytic challenges for predicting clinical outcomes when using multiomics data itself; these are further pronounced when social determinants are added.

The first analytic challenge comes from the high-dimensionality of the data, i.e., the regime in which the number of features is much larger than the number of samples. The proteomic, metabolomic, and other omics datasets today typically contain measurements for several thousand features, and tens of thousands in the transcriptomic data. At the same time, the

cohort sizes for which such data are available are much smaller, resulting in high-dimensionality of the data. Such settings are vulnerable to “overfitting”, a phenomenon in which any developed prediction model is highly accurate on the training dataset, but performs poorly on the unseen test dataset.[51] There are a number of well-developed dimensionality reduction approaches that address this problem, either by choosing the most relevant subset of features (i.e., “feature selection”) or by projecting them to a new set of features (i.e., “feature projection”).[51] Furthermore, by choosing the subset of most informative features, feature selection facilitates interpretation of data, identifying potentially relevant biomarkers, and thereby offering insights into the biology of a disease. Among the available dimensionality reduction methods, the best approach may depend on the specificity of the dataset at hand.

Another analytic challenge for predicting clinical outcomes in a multiomics setting is the discrepancy in the information content of the datasets. Modalities with more measurements often deprive smaller modalities of a chance to participate in the predictions. This is further complicated by the fact that high-dimensional datasets often include highly correlated measurements and may have a lower information content than a smaller, yet more selective, assay.[5] Several solutions have been demonstrated to be successful in practice. In stacked generalization,[52–54] a prediction model is fit for each dataset (using an adequate machine learning algorithm) and then the outputs of all models are linearly combined using a higher-order model to produce the final prediction. Multiple kernel learning integrates data by calculating individual kernel matrices for each dataset before combining them in the final model.[55] Probabilistic graphical models[56] have also been successfully used for integration in several settings.[57]

The heterogeneity of biological, clinical, and social datasets poses another challenge, often further complicated by the presence of strong predictors among clinical or social data (e.g., African-American race). However, it is neither practical nor effective to build separate multiomics models on all possible patient phenotypes based on social determinants, as such subpopulations can be defined using numerous overlapping factors. Modeling of specific subpopulations decreases sample size, which further complicates multiomics studies resulting in the number of measurements overwhelming the cohort size and increasing the risk of overfitting and false positive discoveries. A creative solution is a recently developed algorithm termed “pliable lasso”,[58] which enables flexibility in the coefficients of the now broadly used sparse modeling technique lasso.[59] Pliable lasso falls into the general class of varying coefficient models.[60] The flexibility in coefficients in pliable lasso is controlled by an external matrix, in this case social determinants, which allow the model to use different combinations of biological measurements based on the population-level data available for a patient or a group of patients. This increases sample size (and therefore, accuracy and generalizability) by avoiding the need to study patient subcohorts in isolation.

Integrating social determinants and biological measurements also provides an opportunity for the identification of interventions based on modifiable factors (or combinations of modifiable factors) to regulate key biological pathways. In such a case, once a pathway of interest is identified, it can be included in a causal model[61–63] together with modifiable determinants to identify an optimized intervention strategy. In addition, we have also utilized

computational drug repurposing algorithms to leverage publically available transcriptomic data to uncover novel therapeutic uses for compounds already developed and evaluated for safety, such as for PTB.[64]

SOLVING THE PROBLEM OF DISPARITIES IN MATERNAL AND CHILD HEALTH

One of the most pressing problems in maternal and child well-being is health disparities.[8] With respect to PTB, the majority of individuals in any population do not experience this adverse outcome. This observation alone suggests that some individuals are more vulnerable to whatever factors (whether biologic or social) might be predisposing them to PTB, and others seem to be resistant and might be characterized as resilient. Although disparity is unlikely to have a single biologic explanation, there are individual differences in biologic causes whether they are related to specific genes, gene pathways, or epigenetic changes in response to some aspect of the exposome.

Nevertheless, the most prominent risk factor in the US for spontaneous PTB is being African-American. Many investigations have attempted to explain this higher rate of PTB disparity among African-Americans compared with non-Hispanic whites.[65,66] However, all efforts have failed to show which markers of biologic vulnerability or social disadvantage might have contributed substantially to this risk disparity.[8] These findings have led many experts to posit the likelihood that individual epigenetic variability is the underlying etiology of complex conditions such as PTB. DNA methylation is one of the most studied components of epigenesis, and yet no clear cause-and-effect relationships have been conclusively identified. Nonetheless, our phenotypes as individuals or as populations must reflect such interactions between our genomes and exposomes.

We[10] and many others[67] have described new discoveries in the basic biology of pregnancy and have revealed the complexities of the interactions (current and ancestral) between genetic and environmental forces. Moreover, we have also described novel analytic approaches that permit the integration of biologic and social determinants of PTB[5] and provide the opportunity for a better understanding of how disparities in PTB occur.[8] Such an integrative effort also offers insights into approaches to prevent or ameliorate such adverse outcomes. It is, of course, possible that, even with effective interventions, a change in disparities will depend upon access or adoption by an individual, an individual's community or society. Without such access to or general acceptance of an effective intervention, the issue of disparities will not be solved by "personalization," but could even be exacerbated.

PERSONALIZED VS. PRECISION MEDICINE

In the end, whatever term may be applied to the current efforts to make care more effective —"personalized" or "precise," or whatever —the notion of "personalized" medicine may seem redundant when it is first considered.[68] It is the acceptance of established knowledge, the abandonment of unhealthy habits, and the willingness to explore novel, as yet untried, approaches that offer hope of potential solutions that will matter. Medicine itself, derived from the Latin word, "*medicus*"—a physician—has primarily been focused on addressing

the ills of individuals and on restoring and maintaining their health. However, Hippocrates advised the physician to consider “air, water, and places” (which in our terminology would be called the “environment”) in assessing the treatment of a patient. This consideration introduces the concept that what is “personal” needs to include the context in which a person lives and those determinants of health that we have designated as social, in addition to those biologic. The two are intertwined and either can be directly translated into the other. A false dichotomy of the two is what is important to avoid. They both serve as potential “levers” for effecting change. “Personalized” medicine should be reconciled with another more popular notion today, “precision” medicine.[69] One could argue that both terms, as well as others that have been introduced, such as “evidenced-based” medicine, are simply slogans without much meaning. In some sense, each of the slogans mentioned is an accurate description of medicine. All that is changed is the knowledge within the respective disciplines and the variety of tools used, and not what physicians have always intended—to prevent disease, heal individuals with diseases, and restore health. It is not clear what antonyms the suggested descriptors of medicine would oppose. Do they imply that physicians might engage in “imagination” medicine or “intuition” medicine? Medicine is typically practiced on the basis of the best information available and guided by the inspired and good judgement of physicians.

There is an underlying body of information derived from epidemiologic studies (from population risk) that allows us to apply a probability estimate to personal risk, which offers some guidance for *de*ductive reasoning. *In*ductive reasoning may need to be applied at times, but is also prone to error. Inductive reasoning can sometimes offer clues, but it still requires “intelligent” guessing. Moreover, any such preliminary efforts for greater precision will inevitably be costly. But once precision is established, it may lead to measures that eventually would become less costly, promote health, and serve as a springboard to more desirable outcomes. This point is worth making because “precision” medicine has been accused of accomplishing solutions that are very expensive, but make only minor differences in the outcomes or no differences at all for a population.

The point, however, is that it may well be worth it to become more precise, whatever its current cost, because it would become more accessible eventually, by offering cures and improving a particular outcome for an individual, community, or population. Once this happens, costs may decrease, and the saving of lives and restoring health are justifications enough. Of course, when it comes to reproductive health, the issue is not simply saving lives or even longevity, but assurance of a healthy newborn and a healthy mother. Progress does follow and costs go down, as drugs become cheaper and new diagnostic steps become available. However, new therapies that are more effective may well be more expensive. The solution may be that we strive to achieve precision, wherever possible, but we may have to temper this effort with the assessment of the costs and a possible initial conclusion that some less precise methods, but cheaper ones, may achieve the same desirable results, simply by their being applied on a larger scale (i.e., deliberately in excess).

Those who are adamantly opposed to precision medicine argue that it may well be of some benefit, but such benefits are only for the few; whereas, other efforts (call them less sophisticated) are cheaper, easier to apply, and far more effective for many. We would agree

with this premise, of course, citing food fortification with folic acid as one example and smoking cessation as another. However, organ transplantations and immunotherapy and other molecular maneuvers must continue, even if public health measures save more lives. Medicine is inherently antievolutionary, because it does not stress survival of the fittest. It makes possible for those less fit to survive. Some may refer to this as civilization. The argument that these expensive methods save, prolong, or improve lives for only a few is a matter of morality. At any rate, in a world where people literally starve to death while others live in opulence, arguments about relative costs are vapid. Thus, we would suggest that a better descriptor of medicine would be “rational” medicine.

PREGNANCY AS THE INITIATION OF A LIFE COURSE AND A MODIFICATION OF ANOTHER

What is unique about personalized (or rational) medicine in maternal and child health is that it is fundamental to the life course approach to precision health—to predict, prevent, and cure precisely.[70] The fetal origin of adult disease is now a popular notion, and there is little doubt that prenatal influences contribute to postnatal conditions that emerge throughout the lifespan. Moreover, both paternal and maternal health are relevant to pregnancy outcomes, and the life course of the fetus certainly begins at conception in ways which are not fully understood. We have suggested before that attention to pregnancy is in our world’s best interest even though the return on investment would likely occur later in the life course of both the mother and the child.

Indeed, political gratification might be delayed, but savings in healthcare costs would ultimately be realized. For example, the increased risk of heart disease in women after preeclampsia[71] could be alleviated or PTB could be decreased on a large scale by decreasing the occurrence of preeclampsia, or at least if babies could be born in a healthier disposition later in gestation, closer to term.

CONCLUSIONS

The practice of rational medicine and maternal and child health requires the integration of biologic and social determinants in our execution of healthcare for individuals, communities, and whole societies. To predict, prevent, and cure precisely will require personalization of healthcare that integrates the social determinants of health and their biological counterparts. Such personalization cannot ignore the legacy of social injustice, which has become institutionalized as structural racism and continues to be manifested in individual misery. However, in order to understand how racism “gets under the skin” and into a person’s biology will require approaches similar to the one that we have described here. Indeed, there may be clues for how to achieve better health outcomes in our characterization of individual, community, and societal resilience. Rational medicine needs a life course perspective and should be practiced as a convergent and transdisciplinary profession, similar to the way it emerged in ancient times, only now with powerful new tools and longer life trajectories to which it needs to attend.

We believe that the search for solutions to the problem of PTB, like many other complex human conditions, will necessarily require a deeper understanding of the complexity of the interactions between biologic and social determinants, using sophisticated mathematical algorithms as a common language linking the various scientific disciplines in a coordinated effort to find the most effective clinical and public health interventions.

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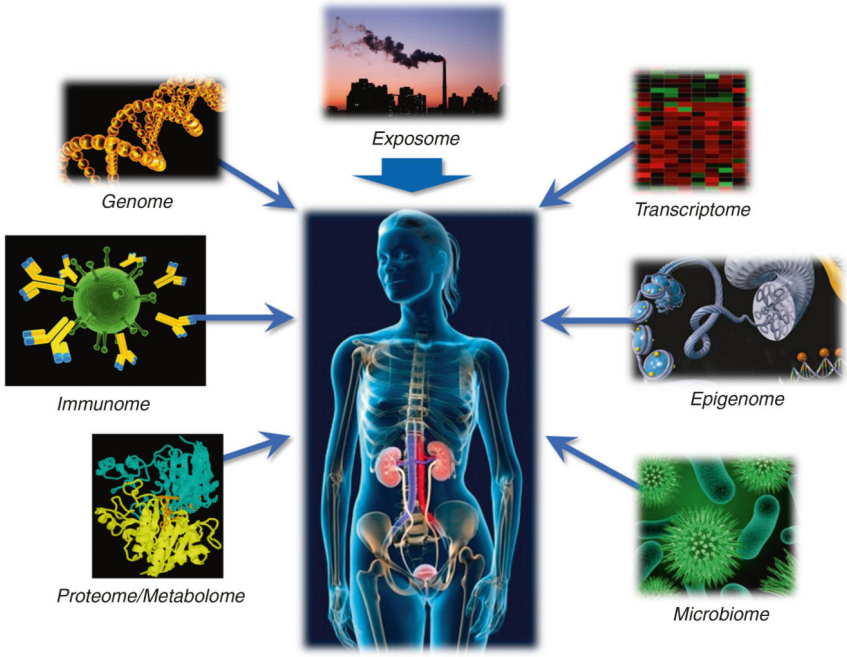

Fig. 1. Integrative personal omics profiling.

The various omics: exposome, transcriptome, epigenome, microbiome, proteome/metabolome, immunome, and genome, whcih can reflect a PTB signature.