Knowledge for Precision Medicine:
Mechanistic Reasoning and Methodological Pluralism

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Precision medicine (PM) describes prevention, diagnosis and treatment strategies that take individual variability into account. While PM aims to incorporate individual variability in genes, in environment and in lifestyle, in current practice the emphasis is on personalized genetic profiling for diagnosis and risk assessment. PM stands to move medicine away from the population-based knowledge that grounds evidence-based medicine (EBM) to the treatment of patients "based upon a deep understanding of health and disease attributes unique to each individual." Such deep understanding requires a broader conception of medical knowledge, the development of new methodologies for generating such knowledge, and approaches for incorporation into clinical practice.

Most actionable genetic variation in individuals derives from extremely rare or even unique variants. Such variants are generally designated as a 'variant of uncertain significance' (VUS). In a medical model that privileges knowledge derived from population-based studies, these variants might be considered variants of unknowable significance, as the extremely low frequency of the variation renders such methods impotent. The strategies required to reclassify such variants will necessarily differ from

those privileged by EBM, given the impossibility of conducting standard population-based analyses. Attempts to determine the significance of such a variant will emphasize mechanism rather than epidemiology. Simple mechanistic reasoning alone may be enough to re-classify a VUS as either benign or pathogenic using a variety of allelic considerations. High-throughput and computational *in silico* analyses can provide predictions regarding the likely significance of a novel variant. Normal protein function strongly suggests a benign variation, while dramatically altered protein function suggests pathogenicity. Family-specific variants affecting multiple, related individuals can be the subject of family cosegregation studies, an epidemiologic approach using Bayesian statistics to calculate the likelihood of a specific mutation being clinically relevant. Even correlation with individual clinical presentation/phenotype may also aid in variant classification, particularly in oncology.

Unlike EBM, PM explicitly prioritizes the individualization of care and focuses attention on unique characteristics of a particular patient. The methods and tools of PM, being developed in large part to help classify rare variants, do not appear in the hierarchies of evidence promulgated within EBM, except occasionally in the bottom tier, categorized broadly as "*in vitro* research" or "mechanism-based reasoning." To realize the goals of PM, the hierarchy of evidence pyramid must be abandoned for a more horizontal conception of medical knowledge. In particular, advancing the field of PM will require acknowledging the value and improving the methods of mechanistic reasoning, including ways to distinguish strong from weak mechanistic reasoning. The value of mechanistic reasoning directly correlates with the soundness of our understanding of mechanisms. As

genomics and proteomics advance, the scope and accuracy of mechanistic reasoning in diagnosis, risk assessment and treatment will continue to improve.

Clinical decision making needs to incorporate knowledge derived from a variety of sources in order to arrive at the best course of action for a particular patient. Clinicians must become comfortable with the "untidy methodological pluralism" developing in medicine, where relevant knowledge comes from a variety of sources and where the value of that medical knowledge varies from patient to patient. Knowledge derived from populations remains informative for clinical decision-making, but is no longer unconditionally privileged over knowledge derived from mechanistic understanding or methodologies. PM demands case-based reasoning, where the relevant particulars of the individual patient must be elucidated and incorporated into clinical assessments and decisions. The major challenge of PM going forward will be to expand the individualized knowledge that can confidently be brought to bear, moving beyond genomics and proteomics to include aspects of lifestyle and environment as promised in its definition.