Precision Medicine: A Pinnacle of Innovation or a Pitfall of Explicit and Implicit Biases?

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Background: The past 5 decades have seen incredible micro- and macroscopic scientific innovations, from the completion of the Human Genome Project (HGP) to the realization of commercial space travel. While there is tremendous excitement about the boundaries of science stretching beyond human imagination, realizing the real-world impact of scientific advancement on the healthcare outcomes of all patients emphasizes just how far we still must go.

The completion of the Human Genome Project[1] has ushered in a new era in our understanding of cancer. We now recognize cancer as a complex set of diseases and understand the vast possibilities of genetically targeted treatment options as well as the way in which existing genetic variations can lead to a high disease risk.

The field of oncology has witnessed rapid strides and perhaps benefited most from an understanding of the complex interaction of epigenetics, environmental factors, and social determinants of health (SDoH)[2]. This field is now seen as precision medicine (PM), or to be more pre- cise, the field of precision oncology and personalized medicine. PM holds the promise of revolutionizing cancer prevention and treatment by combining genotypic, phenotypic, and social factors[3]. The application of PM in oncology permits tailor-made approaches to cancer care,
which increases the chance of achieving treatment response and reducing side effects. The implementation of PM stretches far beyond an individualized approach to cancer care, and in fact, scales to population health with a wider application and larger impact on population health outcomes.
Precision medicine has progressively focused on the sequencing of cancer genomes. This approach has enabled better understanding of onco- genesis and actionable alterations. The technique of next-generation sequencing (NGS) has reduced the cost of sequencing cancer genomes and spurred development of targeted therapies. The depth and breadth of discoveries and innovations have enabled the detection of somatic driver mutations, resistance mechanisms, germline mutations, and quantification of mutational burden. NGS technology has allowed rapid progress in comprehensive genomic profiling (CGP) and whole exome sequencing (WES) to optimize our understanding of molecular patho- logical processes and appropriate therapeutic options. Additionally, NGS has catalyzed progressive developments in pharmacogenomics by uncovering variation in drug metabolism and by explaining differences in the efficacy and toxicity of similar regimens in ethnically diverse pop- ulations.

Promises of PM: Precision medicine is "an approach to disease treatment and prevention that seeks to maximize effectiveness by taking into account individual variability in genes, environment, and lifestyle" according to the Precision Medicine Initiative (PMI) Work group[4]. The goal of PM is to advance medical and scientific discoveries to offer more tailored, precise, and accurate health interventions. This will help maximize health benefits for patients[5, 6]. PM adopts diverse strategies in cancer medicine tailored to the unique biology of a patient's disease. These strategies include application of NGS (either CGP, WES, and/or pharmacogenomics) to identify mutations followed by the use of targeted ther- apies to select site-agnostic treatment approaches. PM's importance is growing rapidly and significantly at a pace faster than healthcare sys- tems can adapt. In order to fulfill the desired goals and objectives of PM, the oncology ecosystem needs to carry out comprehensive strate- gies to achieve success. PM holds the promise of improved efficiency, better care, reduction of ineffective treatments, and the reduction of costs. However, there are potential pitfalls and healthcare inequities that may minimize the global application and benefits derived from a PM approach.

Challenges and Pitfalls in the Implementation of the PM: The pitfalls and shortcomings of PM are multifactorial and include biologic, economic, and psychosocial characteristics. In addition, existing structural racism as well as implicit and explicit biases exacerbate unequal access to clinical trials. These obstacles demonstrate that the realization of PM necessitates cooperative, multidisciplinary, and global efforts. These efforts must stem from biomedical researchers, biostatisticians, community and academic clinicians in collaboration with governments, phar- maceutical industries, social scientists, population health experts and private industries.

- **Lack of Appropriate Representation of Minorities in the Genome-Wide Association Studies (GWAS)** It is essential to develop a comprehensive catalog of mutations unique to each race and ethnicity to accurately represent the world's population and allow PM to benefit all populations equally. A 2017 study examined the populations included in genome-wide association studies (GWAS), the most common type of research that detects genetic alterations associated with disease risk. This study found that nearly 80 percent of individuals in GWAS were of European descent, 10 percent were of Asian descent, 2 percent were of African descent, 1 percent were Hispanic, and less than 1 percent comprised other popula- tions[7]. Health-care inequalities could be worsened through increased use of PM due to racial disparities in access to care. Failure to address sys- temic bias in health-care provision and genetic databases will worsen existing inequities. To prevent this, precision medicine needs to integrate and recognize social and economic influences among ethno-racial groups. For precision oncology to explain and overcome disparities, researchers need to venture beyond the genome to chart the socioeconomic landscape that governs an individual's health.

- **Lack of uptake of NGS testing in a Clinical Setting** In a report published in 2020[8] which measured the use of NGS testing in 1,007 advanced non- small cell lung cancer patients, the use of broad-based NGS testing increased from 13% in 2017 to 26% in 2019 across over 100 oncologists. How- ever, even in 2019, almost 75% of patients with NSCLC did not receive appropriate testing to identify actionable mutations. These figures are even worse among black patients (14% versus 26% overall) showing that despite the promise of PM, it has not been fully adopted in the clinical setting and has been used even less frequently in minority populations.

- **Payer-Related Factors: Limited Coverage/Health Policy** Payer policies are frequently a hindrance for access to testing. In a study published in the JCO-Precision Oncology, Hsiao et al[9], reported that limited coverage and low reimbursement for NGS testing remain huge barriers to NGS imple- mentation. Broader reimbursement policies are needed to adopt pan-cancer NGS testing into clinical practice. . Additionally, NGS testing is not covered equally across all health care insurances.: Medicare oftens covers this testing; however, commercial insurance and Medicaid are often more restrictive in their coverage.

- **Physician and Health Care Team education:** Rapid development of NGS technology and molecular profiling in oncology has not been matched with appropriate provider education. A recent survey found that community oncologists used gene profiling in 33% of lung cancer cases[10]. The study also found a knowledge gap with regard to tumor profiling. Additionally, 69% of respondents were not familiar with matching targeted thera- pies to mutations. Physicians also continue to struggle to manage the large amounts of data with unclear therapeutic significance produced by comprehensive genomic profiling.

- **Social Determinants of Health** Ethnically diverse populations suffer from a lack of access to adequate cancer diagnosis and treatment. This includes reduced screening rates and staging at diagnosis along with the financial challenges people often face following a diagnosis of cancer. There is a need to study the impact of social determinants of health (SDoH) and address them appropriately. Failure to address these will lead to drug development processes lacking demographic diversity in clinical trials. This can further contribute to disparities in care and health outcomes in ethnically diverse populations.

- **Confusion Between Multiple diagnostic technologies** Providers, patients, and payers are somewhat disadvantaged in choosing the right test at the right time. This is due to the wide variety of tests available, such as NGS testing, lab-developed tests, and significant variations in bioinformatic platforms. Single gene testing based on immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH) are often initially preferred by pathologists who have first access to tissue; this leads to exhaustion of tissue for additional testing with NGS, potentially depriving patients of appropriate treatment. However, liquid biopsy will eventually address this challenge in the majority of cases with concordance studies.

- **Pharmacogenomics** The rapid pace of NGS testing and Just-In-Time trials aimed at developing targeted therapies have somehow outpaced appropriate pharmacogenomics inclusivity. As a result, the most significant problems which patients receiving chemotherapy encounter are the development of drug resistance and severe side effects. The variability in the therapeutic responses even in targeted therapies can be explained by individual genetic variations specific for each person. Pharmacogenetic progress can be the keystone to revolutionizing cancer therapy. Introducing patient genotyping into the clinical setting can facilitate decision-making regarding chemotherapy regimens and drug dosages with maximal effect and minimal risk of toxicity. Pharmacogenomics remains the key to unlocking the full potential of PM in cancer treatment.

- **Germline testing** Genetic factors play a key role in the risk of developing several cancers. The detection of a germline predisposition to cancer can impact treatment decisions, risk-reducing interventions, cancer screening, and testing in patients and their relatives. Multiple studies[11,12]have validated the role of germline testing and actionable interventions; however, the uptake of universal germline testing remains low across all sectors.

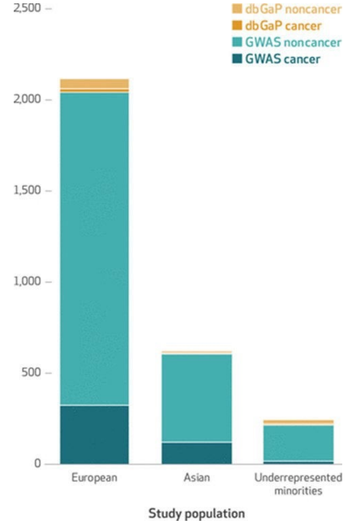

Fig. 1: Quantification of genome-wide association studies and genotype and phenotype studies conducted in 2017 for European, Asian, and underrepresented minorities. This data is sourced from the Genome-Wide Association Study Catalog and the database of Genotypes and Phenotypes (dbGaP). [7]

Discussion: In order to fulfill the promises of PM, i.e. the right care delivered to the right patient at the right time, actionable solutions to the barriers above should be addressed and implemented. Some initial suggestions for further exploration are outlined below. Ultimately, making meaningful change will require a multi-stakeholder team across providers, payers, governments, patients, and industry to boldly create partnerships and solutions in order to close gaps in health inequalities and fully harness the promise of precision medicine.

- Utilize a universal approach to diagnostic technologies, preferably whole exome sequencing or comprehensive genomic profiling, to identify both the somatic mutations and homologous repair defects
- Establish a consensus on guidelines between different specialists, particularly pathologists, molecular scientists, and oncologists
- Establish clinical value, validity, and utility of NGS
- Establish approach to universal germline testing
- Establish concordance between tissue and liquid biopsies
- Establish concordance between MRD (minimal residual disease) and imaging studies
- Apply a data-driven approach to clinical trial feasibility and patient screening
- Accelerate the adoption of new drug approvals using Just-In-Time trials
- Generate new evidence in collaboration with leading health systems, life sciences, and the FDA
- Develop bioinformatics and analytics to transform real-world data into patient care

References:

1.Collins FS, McKusick VA. Implications of the Human Genome Project for medical science. JAMA. 2001;285(5):540–4
2.Matthew Asare, PhD, Marie Flannery, PhD, RN, AOCN®, and Charles Kamen, PhD, MPH. So- cial Determinants of Health: A Framework for Studying Cancer Health Disparities and Mi- nority Participation in Research. Oncol Nurs Forum. 2017 Jan 2; 44(1): 20–23
3.National Institutes of Health. What is PM? https://ghr.nlm. nih.gov/primer/PM/definition. Published 2015. Accessed September 8, 2021,
4.PMI Working Group. The Precision Medicine Initiative Cohort Program - Building a Research Foundation for 21st Century Medicine [Internet]. National Institutes of Health; 2015. [Accessed April 19, 2021. Available from: https://www.nih.gov/sites/default/files/research-training/initiatives/ pmi/pmi-working-group-report-20150917-2.pdf.
5.Collins FS, Varmus H. A New Initiative on Precision Medicine. N Engl J Med. 2015;372(9):793–5.
6.Ashley EA. Towards precision medicine. Nat Rev Genet. 2016;17:507
7.Latrice G. Landry, Nadya Ali, David R. Williams, Heidi L. Rehm, and Vence L. Bonham; Lack Of Diversity In Genomic Databases Is A Barrier To Translating Precision Medicine Research Into Practice; Health Aff (Millwood) 2018 May;37(5):780-785
8.Hinco J. Gierman et al. A retrospective three-year analysis using real-world data on uptake of broad-based NextGen sequencing panels in community oncology practices. JCO.Vol 38;15:e e13668
9.Hsiao et al, Clinical Utilization, Utility, and Reimbursement for Expanded Genomic Panel Testing in Adult Oncology. JCO Precision Oncology. Volume 4; 4:1038-1048.
10.Singh BP, Britton SL, Prins P, et al. Molecular profiling (MP) for malignancies: knowledge gaps and variable practice patterns among United States oncologists (onc). Presented at: 2019 American Society of Clinical Oncology Annual Meeting; May 31- June 4, 2019; Chicago, IL. Abstract 10510.
11.Jiang W et al. Universal germline testing among patients with colorectal cancer: clinical actionability and optimized panel. http://dx.doi.org/10.1136/jmedgenet-2020-107230. Accessed September 8, 2021
12.Edward D. Esplin, & N. Jewel Samadder. Comparison of Universal Genetic Testing vs Guideline-Directed Targeted Testing for Patients With Hereditary Cancer Syndrome. *AMA Oncol. 2021;7(2):230-237. doi:10.1001/jamaoncol.2020.6252. Accessed September 8, 2021*