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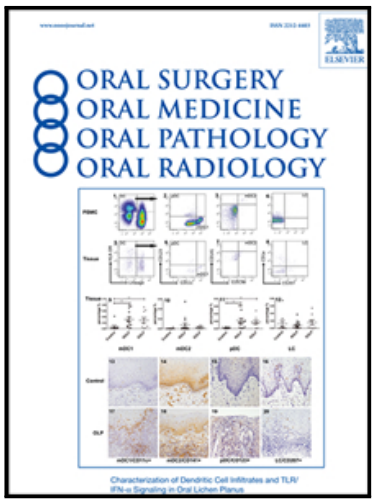

Accounting for diversity in rare disease research and precision medicine

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PII: S2212-4403(19)31601-3
DOI: https://doi.org/10.1016/j.oooo.2019.11.016
Reference: OOOO 4278

To appear in: *Oral Surg Oral Med Oral Pathol Oral Radiol*

Received date: 24 November 2019
Accepted date: 25 November 2019

Please cite this article as: Faizan Alawi D.D.S. , Accounting for diversity in rare disease research and precision medicine, *Oral Surg Oral Med Oral Pathol Oral Radiol* (2019), doi: https://doi.org/10.1016/j.oooo.2019.11.016

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Declaration of Competing Interest

None reported

Word count: 869

We live in an age where the concept of precision medicine is no longer aspirational but it is now institutionalized; not only being used in clinical practice but also helping to drive novel research. The National Institutes of Health (NIH) defines precision medicine as “an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment and lifestyle of each person.”[1]

Tabor and Goldenberg[2], authors of a recent publication in the American Medical Association Journal of Ethics, addressed potential concerns of how increasing use of precision medicine may ultimately create new subcategories of patients based on the relative population frequencies of their genomic variances. The authors suggested that research initiatives and novel therapies are likely to be designed primarily for individuals who have more frequently occurring genetic variances, thereby creating treatment challenges and health outcome disparities for patients diagnosed with “common” diseases but who have rare genetic variances associated with them. Tabor and Goldenberg further opined how the evolution of precision medicine can be shaped by lessons learned from those invested in the care and research of persons with rare diseases.[2]

Several million people live with diseases that are so unusual and uncommon that they may often go years without appropriate diagnosis. In contrast, there are other rare diseases that are well-recognized, yet there has been only limited understanding of their pathogenesis and/or limited efforts made towards the development of targeted therapies. Owing to the rarity of these diseases, it remains a challenge long-recognized by clinicians, scientists, and patient advocacy groups to convince governmental agencies and companies to provide the resources needed to study them, and to

develop effective and affordable therapies. However, the challenges are even more extensive when ethnic and geographic variations are taken into consideration.

Down syndrome is a rare but well-recognized disorder with an estimated 250,000 people living in the United States each year, and an estimated 6000 new diagnoses made annually.[3] A 2002 study published in Lancet demonstrated that mortality associated with this disorder was significantly greater in non-whites, and that this marked racial disparity in survival began early in infancy and persisted throughout childhood and into adulthood.[4] The authors further noted a median life expectancy that was two-times higher in whites compared to African-Americans, and significantly higher than the racial disparity seen across the general United States population. Subsequent population-based studies further confirmed these striking health disparities in people with Down syndrome.[5] The underlying causes of these significant disparities remains unknown, but data suggested that it was likely not the result of comorbities associated with the disorder.[4]

The All of Us Research Program, previously known as the Precision Medicine Initiative Cohort Program, was announced in 2015 and is currently being administered by the NIH in collaboration with an array of hospitals, academic institutions and other healthcare partners.[6] The goal of this ambitious program is to collect health and genetic information from at least one million volunteers; enrollment officially began in May 2018. A major emphasis of the All of Us Research Program is to recruit individuals from diverse backgrounds since it is well-recognized that racial, ethnic, geographic, and economic diversity are variables known to influence health outcomes, and individuals from diverse backgrounds continue to be underrepresented in discovery-type studies.[7]

Similarly, the U.S. Department of Health and Human Services Food and Drug Administration (FDA) encourages broadening eligibility criteria in clinical trials to ensure inclusion of diverse populations that are more representative of the patients who will likely use the drugs after their approval.[8] In June 2019, the FDA published a "draft guidance" entitled "Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs".[8] The goal of these institutionalized initiatives is to provide a framework and mechanisms to overtly account for diversity in the study and development of new therapeutics for commonly occurring diseases. Yet a persistent concern is how to reduce the recognized health disparities among those who live with rare diseases since it's unlikely that these largescale initiatives will capture this population of patients.

To realize the full potential of precision medicine, Tabor and Goldenberg suggested that practitioners should think "small and rare and be proactive" in order to limit unexpected consequences.[2] Those invested in the study and care of patients with rare diseases have likely always had to use this type of approach. Yet, when it comes to understanding the impact of diversity on health outcomes in this unique population of individuals, we may need to think big or at least bigger. As scientists and clinicians with a unique focus on rare diseases affecting the oral and maxillofacial complex, readers and contributors to *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology* are in a position to help shape the narrative and drive the discourse. Through the development of international collaborations, cases and resources can be pooled to help provide greater insight than any single case or report might accomplish. Moreover, by being intentional with inclusion of ethnic, geographic and socioeconomic considerations,

additional important insights might be gleaned that could help inform future study design and therapeutic approaches used for patients with rare diseases. It may also help further the intersection if not eventually unify the goals and outcomes of precision medicine and rare disease research and therapy.

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