Clinical Utility and the role of widespread and broad based pan-cancer germline testing (outside of current guidelines) in community cancer clinic clinics: Part of path to address cancer health disparities:

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Background: 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 precise, 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. While rapid strides have been possible with application of NGS and complete genomic profiling, dissemination of knowledge in germline testing is somewhat crippled and has not achieved much attention despite the fact that is can play a significant role in addressing disparities.

Germline genetic variants that impact cancer risk, prevention, and treatment strategies are implicated in up to 20% of cancers: only a fraction of people at risk for hereditary cancer syndromes undergo diagnostic genetic testing. Barriers to testing, at both the patient, payer, systemic (narrow guidelines and a mandate by some of the payers to have genetic counsellors recommend and approve the test) and provider levels, include gaps in knowledge and poor access to specialty genetics services. The need for genetic counselors to approve the tests while there is an acute shortage of qualified genetic counsellors willing to work in rural underserved areas in itself is a barrier to access to appropriate testing and can result. More than 10% of patients with GI cancer have a germline cancer susceptibility gene variant, which can affect their cancer treatment and/or risk of future primary malignancies. Universal genetic testing of a pan-cancer patient population revealed that 15% of patients (44 of 284) carried a PGV in a cancer susceptibility gene, and that over half (23 of 44) of those with PGVs failed to meet current guidelines for clinical genetic testing. The clinical actionability associated with expanded panel testing has demonstrated its potential to alter patient care. Testing for inherited pathogenic/likely pathogenic variants among cancer patients can provide important information that can have implications for family members and potentially guide treatment decisions and longer-term screening for second cancers.

Needs assessment for broader access to germline testing to address disparities

Despite minimizing barriers to genetic testing, non-White patients were less likely to receive recommended cancer genetics follow-up, with potential implications for oncologic care, cancer risk reduction, and at-risk family members. In patients diagnosed with young-onset CRC, racial/ethnic differences in referral to and receipt of germline genetic testing. We do not understand true biological variations in disease patterns in malignancies based on racial/ethnic backgrounds. Further, if patients are not adequately genotyped, they may miss opportunities to participate in precision medicine or clinical trials and/or elect risk-reducing strategies to prevent a second malignancy.

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 2016 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, 14 percent were of Asian descent, 3 percent were of African descent, 1 percent were of mixed ancestry, and less than 1 percent comprised other populations[7,8] (Figure 1). Health-care inequalities could be worsened through increased use of PM due to racial disparities in access to care. Failure to address systemic 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.

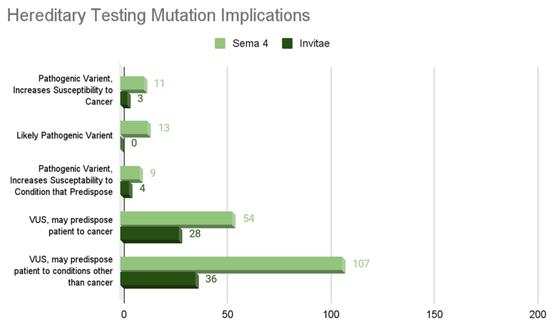
Needs assessment of germline testing unique to disease process

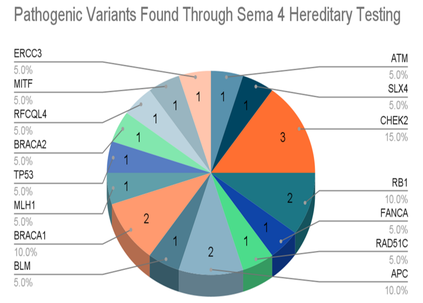
1)Identify congenitally acquired germline inherited mutations leading to multiple cancer in subsequent life and family members, disease course and prognosis 2) Identify pan cancer mutations 3) Identify outcomes differences based on race 4) Correlate to SDoH 5) Create appropriate family members' screening, trace back approach, 6) Identify difference in prevalence of mutations

Methods: We performed germline testing, outside of guidelines, as a part of real world evidence registry to identify prevalence of inheritable mutations with ethnically diverse patient population in rural and suburban population in South Carolina as a part of addressing cancer health disparities (CHD) in patients presenting at earlier age or with either rare tumors, or recurrent/multiple malignancies. This prospective, observational cohort included a suburban and rural underserved population where approximately 30% identify as African American. Patients were counselled and subsequently consented about testing that performed outside of guidelines. Their consent was obtained after explaining in elaborate detail. We developed prospective registries with IRB approved protocol, supported by two labs (SEMA4 and Invitae)

Results: We identified 265 individuals outside the guidelines concordance, compromising of 63% male and 37% female patients within 18 months of this prospective, observational cohort. Patients reported race as African American (71), White (182), or Asian American (12). Rare germline findings included Li Fraumeni syndrome, Fanconi's syndrome, Perelman's disease, and Von Hippel Lindau's disease. We summarize our findings in the attached table

Results (Cumulative)





RTEL1: 6	SLX4: 5	RECQL4: 5	FANCM: 5	RAD50: 4	BRCA2: 4
ALK: 3	EGFR: 3	ERCC5: 3	MRE11: 3	FANCI: 3	ATM: 3
CTC1: 3	PALB2: 2	ERCC2: 2	XPA: 2	AXIN2: 2	FANCA: 2
RB1: 2	BRIP1: 2	NTHL1: 2	MSH3: 2	FANCF: 2	TSC1: 2
TSC2: 2	POLH: 2	BRCA1: 1	DICER1: 1	ERCC4: 1	FANCE: 1
SUFU: 1	DXC1: 1	DDB2: 1	BAP1: 1	RADS1C: 1	RUNX1: 1
MLH1: 1	CEBPA: 1	BARD1: 1	MUTYH: 1	FANCD2: 1	TP53: 1
CHEK2: 1	XRCC2: 1	FH: 1	WT1: 1	PTCH: 1	STK11: 1
DIS3L2: 1	XPC: 1	BLM: 1	TFNF2: 1	ERCC4: 1	FANCL: 1
MSH2: 1	FANCG: 1				

Discussions: Inherited cancer predisposition was believed to be rare until s supposedly rare, as a very small number of patients undergo germline testing. Majority of data of inheritable mutations is limited to Northern European Ancestry and hence our knowledge and awareness as well as identifying mutation if it is truly deleterious or Variant of Uncertain Significance is quite limited due to lack of representation of ethnic minorities in such studies. Multiple publications have identified and emphasized the importance and relevance of need for much more broad access to germline testing outside of existing guidelines.

There is large phenotypic variability in expression of inherited cancer syndrome. This variability can be explained by factors such as allelic heterogeneity, environmental effects, or the presence of mutations on two or more inherited cancer genes in the same individual (defined as MINAS). While past literature reports that inherited mutations are thought to play a role in about 5-10 % of all cancers, recent publications, including a large study carried out at Mayo (INTERCEPT), reported the prevalence of pathogenic variants in germline mutations as high as 28% in certain cancers. Combining these reports in literature and additional factors like environmental influences (including the impact of the social determinants of health) there can lead to the detection of more than 50 hereditary cancer syndromes with different phenotypic expressions. The standard clinical practice for guidelines in concordant testing has it's its own limitations. After detecting a mutation in a specific gene, the clinician may attribute any tumors that are not typical of the detected syndrome to phenotypic variability. Thus, the patient may receive suboptimal treatment and any risks to relatives might be incorrectly estimated go undetected. Studying patients with multiple mutations in different cancer syndrome genes could provide insights into how the functions of the relevant genes products may be related and result in an enhanced or novel phenotype. 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[12,13]have validated the role of germline testing and actionable interventions; however, the uptake of universal germline testing remains low across all sectors.

Factors limiting access to widespread germline testing:

Need for Genetic Counselors to approve and/or recommend testing: Due to post pandemic shrinkage in healthcare work force as well as even pre pandemic times, there has been a shortage of genetic counselors particularly in underserved rural communities. We therefore feel that an oncologist well trained in interpretation and management of germline testing implications may be appropriate decision-making individual to ensure that CHD may not worsen due to lack of access to germline testing.

Narrow scope of guidelines and pathways

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 [10], reported that limited coverage and low reimbursement for NGS testing remain huge barriers to NGS implementation. 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 often 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. Physicians also continue to struggle to manage the large amounts of data with unclear therapeutic significance.

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

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