Genomic Medicine 5
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Hyatt Regency Bethesda, Bethesda, MDs

Introduction

The goals of Genomic Medicine V are to engage federal stakeholders in discussing potential overall US strategies for eventual implementation of genomic medicine in routine clinical care. Agencies' perspectives are sought on current needs, gaps, and obstacles to the implementation of genomic medicine relevant to their missions; related activities currently in progress or planned by each agency; approaches for how NHGRI and NIH can facilitate or expand agencies' activities, if desired; and other federal agencies potentially relevant to these discussions. Potential outcomes include a white paper on needs for genomic medicine implementation within the US and approaches for addressing them, a list of commonalities in interests or opportunities across agencies, model use cases, plans for communication and collaborations across agencies, and plans to interact with international efforts in genomic medicine.

US Federal Strategy Efforts – Geoff Ginsburg

Having a cohesive federal strategy would help accelerate the rational implementation of genomics research findings and technologies in clinical care. Such strategies should, among other things, help to standardize and coordinate genomic medicine initiatives across the nation, create public-private partnerships, develop the infrastructure necessary for informatics, and address workforce needs. Nationwide strategic approaches to genomic medicine implementation are perhaps best exemplified by the UK House of Lords' 2009 inquiry into genomic medicine, a extensively researched document that led to a human genomics strategy group report on the implementation of genomic medicine in the UK. They are able to leverage the structure, centralization, and widespread distribution of the National Health Service, as well as strong existing genomics research centers and the UK Biobank repository. The Department of Health recently committed 100 million pounds (~$155M) to this effort. In Canada, the creation of GenomeCanada and its affiliated provincial Genome Centres provides support and coordinated management of science and technology programs in genomic medicine. It recently funded a number of projects in cancer, sequencing, and prenatal screening. In the US, the Institute of Medicine is leading a series of roundtable discussions on translating genomic-based research for health. They have now developed reports in the areas of molecular diagnostics, drug discovery and development, and genomic medicine and public health.

The group agreed that any US genomic medicine strategy should ensure equal access to care for all. The military services' focus on improving performance and readiness provides a somewhat different perspective over civilian medical care needs. They do not have the EMR and decision support power that the VA and many academic institutions have. The Office of the National Coordinator for Health Information Technology (ONC-HealthIT) would be an important group to take HL7

standards and make them interoperable and usable by all. The Clinical Decision Support Consortium (CDSC) funded by AHRQ could also provide some guidance though their program comes to an end soon.

One important issue is how to convene all of the relevant agencies and professional societies. Previously, the Secretary's Advisory Committee on Genetics, Health, and Society was the unifying body, but now we have nonbinding groups convened by IOM. Some sort of charter or constitution could help unite the groups better. We should also try to engage pharma to attend, as they played a large role in getting Genome Canada off the ground.

CAP Genomic Policy Framework – Debra Leonard

The College of American Pathologists (CAP) has created a white paper making recommendations for 12 issues in genomic medicine. These include basic infrastructure, payment, ELSI, and defining the role of pathologists in coordinated genomic medicine delivery. One fairly universal concern is ensuring that clinicians order the correct test, with an example giving of physicians ordering sequencing when a specific biochemical assay was indicated. Marc Williams is leading an effort to explore this issue through NHGRI's Genomic Medicine Working Group (GMWG) and the payers' meeting it convened. CAP also identified patent issues as a concern and suggested the Patent Office as a federal agency that should be engaged in these discussions.

The military representatives noted they are currently engaged in bringing the various health care systems of each branch together and creating a unified EMR system. The military representatives also noted that many projects have contacted the military to use its resources in the guise of providing benefit to the branches.

Genomic Medicine at NHGRI – Teri Manolio

Since the creation of NHGRI's 2011 Strategic Plan, the implementation of genomic medicine has received increased attention in NHGRI's research programs. Relevant projects include these Genomic Medicine meetings, the eMERGE Network's collaboration with the Pharmacogenomics Research Network (PGRN) on a pharmacogenomics pilot project, the Clinical Sequencing Exploratory Research (CSER) program, the Clinically Relevant Variants Resource (CRVR), and the Inter-Society Coordinating Committee on Practitioner Education in Genomics that grew out of the fourth Genomic Medicine meeting. NHGRI has already engaged Cecili Sessions's Air Force project as an affiliate member of eMERGE, and it could consider similar options for other federal agencies. Many NHGRI programs are looking at issues of clinical utility, including the eMERGE genomic medicine pilots and the new Newborn Sequencing programs.

Department of Veterans' Affairs – Larry Meyer

The VA health system serves about 7 million patients every year across the country. All VA centers use the same EMR system, though records from individual sites are not readily interoperable. The VA's Genomic Medicine program was established in

2006 to enhance clinical care for veterans and develop processes to integrate research results into care. Many providers provide genetic care with complex cases going to academic affiliates. The Million Veterans' Program has been an important step forward in the research arena, but the clinical program has lagged. The VA has now created a National Clinical Genomic Medicine Service which will allow genetic counselors to conduct teleconsultations and electronic consults across the country. Their current needs include integrating lab data, family histories, and clinical decision support into EMRs and creating processes for evaluating clinical utility across a large population. The VA has three large projects ongoing – implementation of Lynch syndrome screening, integration of Lynch syndrome services for those with colorectal cancer, and communication of probabilistic information. The strengths of the VA system are a wide range of specialty and generalist care, diverse socioeconomic and health literacy levels, and its EMR and informatics. They are building data sets with full patient records and trying to better understand health history documentation using Natural Language Processing (NLP). There is no obvious catalog of genomic medicine research in the VA but Ron Przygodski offered to provide a list.

US Air Force – Cecili Sessions

The Air Force PC2-Z program focuses on bioinformatics, education, research, and policy to enhance military readiness, improve healthcare, and mitigate costs. Current obstacles include the inability to order lab-designed tests, data privacy and protection, operational relevance of genomics, ELSI, and lack of coverage of the military under GINA. The Precision Care Advisory Panel hopes to evaluate translational science and provide output, such as a version of GINA for the military. While the military has good EMR capability, large populations, and standardized systems of care, it does not have a large community of researchers. One way civilian sites could collaborate with the military might be to enable civilian access into the military system and have them use tools within the military's framework. Collaboration with military investigators may be necessary to ensure at least one collaborator is subject to institutional sanctions. Appropriate policies against wrongdoing need to complement any data privatization methods. The initiation of the trans-service Defense Health Agency (DHA) on October 1 should facilitate research and implementation in the large populations DoD cares for; information technology will be a key component of DHA's portfolio.

Centers for Medicare and Medicaid Services – Steve Phurrough

Medicare has 4 requirements for payment for a service: 1) it must be legal, 2) Congress must give permission to pay for it, 3) it must be "reasonable or necessary", and 4) it has appropriate coding and payment instructions. Preventative screening was not paid for until recently. Most services that CMS pays for need studies showing clinical utility. However, perceptions of what clinical utility is differ within CMS. CMS can either make a national decision to pay for a test, or a local CMS branch can make a decision that the rest of the country then follows (which has happened with many lab-developed genetic tests). Broad guidance is provided to contractors in making decisions about coverage with regard to clinical utility but

this is not standardized. At a federal level it's more concrete and generally involves a change in management or outcomes. Payment and coding both have complexities that have made genetic tests hard to cover. The BRCA test is paid for as a diagnostic, but not as a screening test. Genetic counselors and PhD geneticists cannot bill separately at present. Further discussion revealed that Blue Cross/Blue Shield has more consistent definitions of clinical utility that essentially involves improving an outcome, but direct evidence of this can be hard to come by.

Food and Drug Administration – Elizabeth Mansfield

Needs in genomics at the FDA include 1) standards, 2) quality systems, 3) curated databases of evidence, and 4) programs to develop evidence. One area for this is databases, as most databases now are well populated but not curated and with little evidence. FDA also wants proper decision support and education tools for clinicians using genomics, as well as quality systems with proper evaluation metrics. Additional goals include widely available standards, systems built with quality metrics, and evidence to drive care. Many companies do not currently seek FDA approval or their tests because doctors will order them regardless. FDA black box labels emphasize that a patient should consider pharmacogenomics for certain drugs, but those who do want to act on it face a barrier to testing. Major challenges in FDA and CMS working together are that their mandates and levels of evidence are very different.

Agency for Healthcare Research and Quality –Carolyn Clancy

AHRQ focuses on patient safety and outcomes research. They are a primary source of data for health care spending. They also support the US Preventive Services Task Force which provides systematic reviews of evidence for consideration. Significant needs include clarifying the benefits and harms of genetic testing and the value of adding genomic tests, to define better what is appropriate use. They also need better systems for feedback from care delivery to science; this provides bidirectional opportunities both to improve the science and to disseminate useful findings directly into care. They have developed cancer registries to support the appropriate use of genetic information and biomarkers. AHRQ's expertise is in patient-centered outcomes research and dissemination; NHGRI should get involved in comparative effectiveness research. The development of value-based metrics will be crucial as we go forward to show the impact of genomics on care.

Office of the Assistant Secretary for Health (OASH) – Anand Parekh and Lisa Lee

The OASH contains offices on different minority health groups, public health, and also the Surgeon General's office. They create the Healthy People health objectives for the nation which recently added two objectives in genomics: the United States Preventive Services Task Force should educate women with a family history of breast and ovarian cancer about BRCA1/2 testing, and EGAPP should establish counseling for patients newly diagnosed with colorectal cancer to get genetic testing.

The Bioethics office created a report called Privacy and Progress in whole genome sequencing to cover five main underpinnings – strong baseline protections while promoting data access and sharing, data security and access to databases, consent, facilitating progress in whole genome sequencing, and public benefit. People thought OHRP needed to do more in the area of ensuring consent from participants. It also needs to take a closer look at the difference between research and clinical spheres. Privacy and data sharing seem to be major issues that can be coalesced around by multiple agencies.

Patient-Centered Outcomes Research Institute – Joe Selby
PCORI was created by the Affordable Care Act. Its research deals with differences in the effectiveness of healthcare treatments across different subpopulations and disseminating those results. They do not fund cost-effectiveness research, but instead fund comparative research for practical purposes. PCORI's research priorities include assessment of prevention, diagnosis, and treatment options; improving healthcare systems; communication and dissemination research; addressing disparities; and accelerating patient-centered outcomes research and methodological research. These four areas have advisory panels including patients for targeting research; the question arose as to whether there should be one in genomic medicine. Patients do not appear to have been thinking about genomic medicine; however, most of the patients they see have multiple conditions and are more worried about having access to care. PCORI is interested in receiving applications in the area of genomic medicine and one specific need would be to develop criteria for evaluating patient-centered research in this area.

Centers for Disease Control and Prevention – Muin Khoury
The CDC works in the area of public health genomics. Their model allows for genomic discoveries to guide the creation of recommendations or policies that govern healthcare systems working in a population's disease prevention. Advanced molecular detection of infections is an area of genomic technology that is a very high priority for the CDC Director. CDC also focuses on "Tier 1" evidence with proof of readiness for application; for example about 2 million people have Tier 1 indications of genomic risk such as BRCA1/2 or Lynch screening and don't know it. We also need to develop an evidentiary case for genome sequencing. GAPPNet served to try to link evidence to practice, integrate it into healthcare, and disseminate it widely. However, it did not succeed because there was no over-arching theme to push, and for most of its 15 years there were very few actionable findings. Better and broader outcomes research could help us gather the evidence needed to judge clinical utility. A key need is for a national assessment of the research questions that need to be answered.

Day 1 Key Issues

Standards/IT infrastructure/interoperability
ONC-HealthIT seems like the most obvious contributor to developing standards for interoperability, but we need to go to them with a list of requests. The Defense

Health Agency – a collaboration across the DoD medical services - would also help unite the disparate IT platforms. Common CDS will be another important unifying factor. We could engage the CDS Consortium or create a common set of rules for each EMR. The military could use the Meaningful Use criteria to help them meet the standards of civilian records. A CDS repository might be helpful for all systems to draw from, though when one gets to actually coding CDS rules in a given EMR system inter-operability is typically lost. Outcomes should be patient-centered as well as system-centered.

Evidence generation

We need to better understand what outcomes we want to study, then see what evidence is necessary to the study them. Different levels of evidence seem to be needed by CMS, private payers, and military (particularly in regard to readiness). Perhaps some kind of national body to grade levels of evidence would be worthwhile, as might some standard criteria for evidence across all agencies, possibly with some allowance for agencies to customize to their needs . It would be helpful to specify whether a finding is actionable or has proven clinical utility, for example, and what evidence is needed for each. We do not need trials for every outcome, but just enough observational data to justify a test's use. Decisions about inclusion of tests in newborn screening panels, for example, use consensus rather than randomized trials. Levels of evidence needed can vary by outcome; in phenylketonuria there is evidence for the value of dietary restriction in preventing seizures and institutionalization, for example, but not for optimal intellectual functioning, One place to start is to analyze the existing CPT codes. Given the differing evidence requirements of regulatory and reimbursement agencies, we are missing engagement of CMS and FDA in developing studies to be sure the design will generate the evidence needed for approval and reimbursement. CMS requests evidence that a test is reasonable and necessary but can't pre-define partly because they need public comment on draft coverage decisions. FDA is willing to work with study designers but asks for "serious inquiries only," those who want their advice and will follow through on it rather than taking their advice and then marketed a lab-developed test. The group wondered if there were higher level principles for designing evidence standards of similar studies such as pediatric screening tests, where sufficiently similar areas would have similar study designs.

Curated databases

Databases like ClinVar and ISCA have experience with creating appropriate infrastructure for clinical data. We will need to engage these groups as we move forward. The Medical Device Innovation Consortium is a precompetitive space for diagnostic companies that we might be able to shift to databases. We also need to create standards for what goes into databases and how to get the data out; it would help to develop standards for that across institutions. Many things currently called databases are really repositories, but it would be useful to have industry standards for what a quality curated database should be, including policies for data curation and data privacy and consent. Eventually, we could add patient outcomes as a data type to these repositories. CMS could require deposition of variant data as

requirement for being reimbursed for these tests, like part of coverage with evidence development as was done for left ventricular assist devices, implantable defibrillators, and PET scanning.

Privacy/data sharing/incidental findings
We need to better define types of findings to be expected, perhaps by reviewing the first 1,000 people sequenced to determine how many reportable findings were identified. This would give data on incidental findings almost for free; in Geisinger's genome sequencing project patients agree to annual contacts and updates of treatments and behaviors. For example, there is a significant difference in actionability for a finding that is clinically useful but unexpected, a finding that is clinically valid but not useful, and a variant of unknown significance. We also need to start thinking about questions of liability as we collect more genetic information that might be understood later.

Policy
We need to have all of the departments moving in the same direction. Potentially we can go back and answer any lingering questions once we have a solid base established. There seemed to be broad agreement on four high priority areas: 1) standards/IT infrastructure, evidence generation, privacy/data sharing, and incidental findings. We could develop working groups to address these areas or design a research project in a large population like DoD or the VA to address them. We could define use cases and distribute to the various agencies, asking which pieces are relevant to each agency. If a number of agencies approached ONC and said we need these standards and here's why, we'd be much more likely to succeed. Writing a paper on why the EGAPP recommendations on Lynch syndrome haven't been achieved would be powerful in laying out a research agenda.

Day 2

Possible Next Steps – Rex Chisholm

- Engage DoD and VA groups in ongoing pilot/demonstration projects
- Engage PCORI about expanding genomic medicine and attracting more genetics applications. Research in return of results may be quite relevant to them as comparative effectiveness research.
- Convene FDA, CMS, and payers to review ongoing pilot projects and develop general principles for sequencing standards and payment plans.
- Collaborate with basic science researchers and sequencing experts (like re-engaging Howard Jacob and the GMII sequencing working group, the Human Genome Reference Consortium, CRVR, and FDA/NIST's Genome in a Bottle) to understand the gaps and needs in sequencing databases and figure out how to make file formats for display in clinical environments in the future
- Discuss national strategy efforts with each agency and detail their goals, resources, and barriers

- Compile list of implementation strategies across federal agencies and find overlaps and deficiencies
- Work with OSTP to discuss technical and policy issues that could be covered in a white paper
- Develop an overarching scheme for coordination of work between agencies to facilitate the creation of a national strategy

American College of Medical Genetics and Genomics Report on Incidental Findings – Les Biesecker

The ACMG initially set out to create a list of incidental findings that should be sought out clinically. These variants would have high penetrance, existing treatments, known pathogenicity, and a long asymptomatic period. They decided on a minimum list of medically important conditions/genes/variants that should be evaluated and returned to clinicians. The clinician who ordered the test then determines when/if/how the result should be returned. The working group felt that variants should be returned regardless of age, because a variant for an adult-onset disease found in a child could be actionable for the child's parents. Patients should not get to choose which disorders they see results for because incidental findings are an inextricable part of sequencing, just as any additional findings found in a CT scan are part of that scan. A medical geneticist or genetic counselor should lead pretest counseling with the patient. ACMG has worked to compile as much evidence as possible for these variants. The report puts the onus on the ordering clinician to have the expertise to interpret the test and explain its implications.

College of American Pathologists Genomic Medicine Policy Framework: Clinical Issues – Debra Leonard

CAP's Genomic Medicine policy framework provides a global perspective for the role of pathologists in genomic medicine and explains how genomic testing can be integrated into practice. Major issues it brings up include interoperability standards, gene patenting restrictions, and reimbursement for interpretation. There is a need for central storage to make it easier to access records for patients who move.

Clinical Sequencing Exploratory Research – Brad Ozenberger

The CSER consortium works to research challenges to applying comprehensive genomic sequence data to the care of patients. Studies have 3 components: clinical study, sequencing/analysis/informatics, and ELSI. After one year, the six studies have consented 455 patients and sequenced 170. The sites vary as to where incidental findings are reported and whether there is opt-out to hear results. Groups intend to return pathogenic variants and variants of unknown significance for primary indications and pathogenic variants for incidental findings. The biggest challenge is determining sufficient evidence for pathogenicity. The newly-funded Coordinating Center is working on issues with CLIA and reimbursement.

Mission Health System – Lynn Dressler

Mission Health is a nonprofit health system that serves about 1 million people in rural western North Carolina. Its leadership includes people from Geisinger and Intermountain Health who want to develop an infrastructure for genomic medicine including education resources, pharmacy, genetics, pathology services, and pharmacogenomics. Most affiliated clinicians have their own private practices. In Phase I, they are trying to establish an IT infrastructure using Cerner. They do have considerable support and buy-in from clinicians in the area. They will be rolling out three pilot projects in pharmacogenomics testing for drugs with FDA black box labels, preemptive testing of CYP2C19 for clopidogrel, and best practices for tumor marker testing and integrated lab reports. They face many challenges, including cost/benefit analyses, informatics development, reimbursement estimates, data storage, and lab performance, but they are actively working through these.

University of Miami Masters in Genomic Medicine – Jeff Vance
The Masters in Genomic Medicine at University of Miami runs concurrently with the MD program in hopes of creating clinicians with adequate genomics education. The program is 30 credit hours over four years using a combination of online modules, group discussions, lab/clinic rotations, and research. They have recruited faculty from many departments who teach fundamentals of genomics, clinical applications, computational methods, research ethics, and diagnostic labs. 5 people are in the first class, and they have already started applying for conferences. The program is free for out-of-state students and an additional $8K for in-state, a significant barrier. Students see the value of this program for residencies and their current medical education. Jeff offered to share some of his PanOP lectures with others.

Pharmacogenomics Research Network – Dan Roden
The PGRN has been in existence since 2000, comprising 14 clinical sites and a coordinating center. The PGRN Pharmacogenomics Knowledge Base (PharmGKB) accrues data on drug/gene pairs and variability of responses. The studies all revolve around implementation, such as Vanderbilt's PREDICT program which integrates point of care decision support for CYP2C19-genotyped patients receiving clopidogrel. They assessed their final antiplatelet therapy after 90 days. The Clinical Pharmacogenetics Implementation Consortium (CPIC) makes guidelines for acting on specific genotypes in certain drug treatment situations, which they have now integrated into clinical care as part of the Translational Pharmacogenetics Project. They have found that the integration process is very complicated and requires strong institutional support and a very active CDS that interprets genetic data and guides clinicians through prescription options. The PGRN also partnered with eMERGE to create a targeted sequencing array for capturing 84 very important pharmacogenes. The eMERGE-PGx project will track performance metrics and healthcare impact. Each site has a different policy on return of incidental findings as part of informed consent.

Inter-Society Coordinating Committee – Teri Manolio
The ISCC was formed after GM5 to address gaps in genomics education for physicians. Professional society representatives discussed how education needs to

be embedded at the point of care, but also needs to incorporate resources like case studies and ethical guidelines. They also noted that these resources should be incorporated into CME courses and certifications and be able to be tailored to subspecialties. Many physicians are reluctant to order tests and have limited knowledge on interpretation and counseling. Physicians have shown interest in genomics but are only willing to commit a small amount of time learning about it. The ISCC has four working groups: the Competencies WG will review surveys and existing competencies and determine the needs of each society, the Educational Products WG will begin to develop resources, the Specialty Boards WG will reach out to boards and determine how genomics can become a greater part of certification, and the Use Cases WG will create model scenarios for distribution to societies. We hope to develop substantive metrics like increased knowledge and use of products. ACMG hopes to create training tracks for cardiologists and oncologists to learn enough genetics for their subspecialty.

Payer's Meeting Follow Up – Derek Scholes

The payer's meeting group has been working in a variety of areas, including a white paper, data sharing issues, research on physician ordering of genetic tests, reimbursement criteria, and an infrastructure for clinical utility research. Ansalan Stewart of HHS is leading a trans-HHS working group exploring how HHS agencies can catalyze clinical use of WGS and WES. The MEDCAC meeting found moderate evidence of clinical validity for tissue tests on cancers of unknown primary site, but little use of utility. The group is also analyzing where to reduce error in genetic testing (typically pre- and post-test). Another interesting issue is the display for reporting of results. Many displays look very ugly and outdated, so it might be necessary to engage graphic designers and other people skilled in this area.

European Science Foundation's Personalized Medicine Launch Event

The ESF has been holding a series of meetings discussing the development of personalized medicine in Europe for disease prevention and treatment. Their goals include the creation of usable datasets, new trial designs for assessing efficacy, patient engagement and stakeholder participation, informatics tools and Cloud sourcing, EMRs, patient rights for managing data, and education. Their initiative is supported by many agencies within and outside Europe. Their initiatives will be rolled out in 3 phases and will be shared with other global agencies.

Genomic Medicine 6 – Geoff Ginsburg

Right now there are genomics hubs in North America, Europe, and Asia, but no global forum for all of these groups to interact and collaborate. In addition to groups we have already heard about in the UK and Canada, the World Economic Forum held a meeting in 2013 on different aspects of personalized medicine. At GM6, we hope to identify common barriers, synergies, opportunities for implementation, policy agendas, and economic analyses. We would hope to develop an international convening organization, as well as some pilot projects, standards for data, and education initiatives.

ACTION ITEMS

1) Teri will circulate the matrix of genomic medicine implementation components to the federal agencies to identify high priority components for collaboration.
2) Laura will explore engaging the Office of Science and Technology Policy in endorsing the development of a federal strategy.
3) NHGRI will work to re-engage the Office of the National Coordinator for Health Information Technology in data standards and interoperability issues critical to collaborative genomic medicine efforts.
4) Jeff Vance will send his lecture videos for the UMiami Genomic Medicine Master's program to NHGRI's G2C2 repository.
5) NHGRI and other agencies should engage DoD and VA groups in ongoing pilot and demonstration projects and future evidence generation programs.