Overdiagnosis, Genetic Screening, and the Primary Care Provider

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Disclaimers

- I have no known conflicts of interest related to this topic.

- I speak for myself and not MDFMR or JAMA.

- Genetics, genomics, personalized medicine, precision health etc. is not going away...
Outline

• The scope of genetic screening/genomics in clinical (primary) care.

• Roles, responsibilities, and appropriate use – what do we know about genome sequencing in the healthy clinic patient?

• Emerging models/next steps.
Seven Questions for Personalized Medicine

Joyner and Paneth, JAMA September 8, 2015 Volume 314, Number 10

Personalized or precision medicine maintains that medical care and public health will be radically transformed by prevention and treatment programs more closely targeted to the individual patient. These interventions will be developed by sequencing more genomes, creating bigger biobanks, and linking biological information to health data in electronic medical records (EMRs) or obtained by monitoring technologies. Yet the assumptions underpinning personalized medicine have not been questioned. In this Viewpoint, we seek to stimulate a more balanced debate by posing 7 questions for the advocates of personalized medicine.

Does the Human Genome Contribute to Disease Risk Prediction?
Personalized medicine builds on the Human Genome Project, which was forecasted to revolutionize disease risk prediction, with projected relative risks as high as 6 for gene variants linked to specific diseases. However, the relative risks for the vast majority of gene variants rarely exceed 1.5, and these variants have added little useful predictive power to traditional risk prediction algorithms. Moreover, improved understanding of lifestyle influences is expected to reduce the provision of genomics risk information to patients who have not materialized.

Will Gene-Based Drug Targeting and Development Fulfill Its Promise?
Personalized medicine predicts that therapies for cancer that target dysregulated “omic” pathways will be transformative. Yet the benefit of such drugs on overall cancer survival has been limited, perhaps because of the adaptive nature of cancer. There is little evidence that targeted therapy will interrupt the cycle of expectation and disappointment that has typified many of the new approaches to cancer therapy. Most of the recent successes in cancer have resulted from the traditional public health measures of screening, early detection, and smoking reduction as well as some immunologic therapies.

For common disorders, the claim that genotype-based treatment schemes will be more effective with fewer adverse effects is not supported by evidence for both tamoxifen and warfarin. Even though gene variant information can suggest new therapeutic targets, it will always have to be integrated into traditional drug discovery approaches.

Two much-publicized successes in disease gene identification were BRCA1/2 for breast or ovarian cancer and mutations for cystic fibrosis (CF). Although finding a subgroup of the population that is at very high risk of cancer is important, no new therapies have resulted from discovery of the mutations. Instead, the 5% of patients with breast or ovarian cancer who are positive for BRCA are offered enhanced screening and preemptive surgery. In the 25 years since BRCA1/2 was discovered, breast cancer mortality in the United States has declined by nearly one-third; however, little of this decline stems from the discovery of BRCA1/2. Moreover, BRCA1/2 is a unique story because the gene variants account for such a substantial amount of the variance in outcome for a limited number of patients.

In CF, 2 drugs (vafaracinar and imucacinar) have recently been developed based on the CF transmembrane conductance regulator gene (CFTR), but they are useful only in patients with specific CFTR mutations, in whom they increase, singly or in combination, maximum forced expiratory volume (FEV) by 5% to 10% and improve weight gain. However, since the discovery of this gene in the 1980s, CF survival has improved substantially as a result of strict adherence to clinical management guidelines originating in pulmonary physiology and infectious diseases, but not genomics.

Although well deserved recognition has accompanied these genetic discoveries, neither has been a significant factor in the substantial reduction in mortality from the 2 target diseases during the past 25 years. The commitment to screening technology and adherence to best practices has proven far more important to the lives of affected patients.

What Will EMRs Contribute?
The transition to EMRs has expanded the reach of medical-record-based information, but has not markedly improved the quality of the data entered. Although examples of improved clinical practice driven by EMR data can be found, the quality and granularity of the data they record limit their use in research. The inherent variability of clinical data across institutions is magnified by institutional-to-institution differences in EMR systems. A seamless, interoperable national EMR system is, at best, decades away for the United States and unlikely to include informative phenotypic data such as waist circumference, musculoskeletal fitness, and exercise capacity.

What Kinds of Studies Should Be Mounted in Personalized Medicine?
In recent years, large-scale unsupervised, agnostic discovery, and data mining have been used to describe an approach to big data that proceeds without explicit hypotheses, with conclusions derived from the patterns of discovered associations. Convenience samples are often used without an appreciation of how selection bias and other factors can distort exposure-outcome relationships. Much so-called discovery science presupposes that the individual is isolated from his or her social context and that cellular data are sufficient to predict disease. By contrast, successful population-based approaches to the study of disease, such as the
Seven questions…

• Does the Human Genome Contribute to Disease Risk Prediction?
• What Kinds of Studies Should Be Mounted in Personalized Medicine?
• How Will Personalized Medicine Affect the Costs of Medical Care?
• Where Is the Public Health Benefit?
Scope of Genomics?

What are you “screening” for?
- Disease risk?
- Pharmacologic risk or benefit?
- Reproductive risk?
- Risk to family members?
Scope of Genomics?

What is a “screening” test in the context of genomics/precision health?

- Is it a family history?
- A biochemical assay?
- A single genetic test?
- A panel of genetic tests?
- The entire genome?
Scope of Genomics?

What is the context of “screening”? 
- Primary, population based?
- Primary, clinic based?
- Targeted, clinic based?
- Secondary, clinic based?
- Opportunistic (e.g. DTC)?
Scope of Genomics?

What is the desired benefit/value from “screening”?

- Mortality decrease?
- Morbidity decrease?
- Decreased cost?
- Knowledge gain?
- Increased income?
Scope of Genomics?

Who derives benefit/value from “screening”?

- Individual?
- Family?
- Clinical entity?
- Biotech industry? (2% GDP in 2012* )
- Insurer?
- Employer?
- Society?

Carlson R. Nature Biotechnology 34, 247–255 (2016)
Scope of Genomics?

In genomics, one person’s overdiagnosis may be another person’s idea of an “actionable variant”...
Scope of Genomics?

1) An EBM-oriented perspective…
… where genomic screening might stand alone.
The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: methods of the EGAPP Working Group

Steven M. Teutsch, MD, MPH, Linda A. Bradley, PhD, Glenn E. Palomaki, BS, James E. Haddow, MD, Margaret Piper, PhD, Ned Calonge, MD, MPH, W. David Dotson, PhD, Michael P. Douglas, MS, and Alfred O. Berg, MD, MPH, Chair, on behalf of the EGAPP Working Group

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative, established by the National Office of Public Health Genomics at the Centers for Disease Control and Prevention, supports the development and implementation of rigorous, evidence-based processes for evaluating genetic tests and other genomic applications for clinical and public health practice in the United States. An independent, non-federal EGAPP Working Group (EWG), a multidisciplinary expert panel selects topics, oversees the systematic review of evidence, and makes recommendations based on that evidence. This article describes the EGAPP processes and details the specific methods and approaches used by the EWG.

Key Words: Evidence-based medicine, review, systematic.

The completion of the Human Genome Project has generated enthusiasm for translating genomic discoveries into testing applications that have potential to improve health care and usher in a new era of “personalized medicine.” For the last decade however, questions have been raised about the appropriate evidentiary standards and regulatory oversight for this translation process. The US Preventive Services Task Force (USPSTF) was the first established national process to apply an evidence-based approach to the development of practice guidelines for genetic tests, focusing on BRC1/2 testing (to assess risk for heritable breast cancer) and on HFE testing for hereditary hemochromatosis. The Centers for Disease Control and Prevention-funded ACCE Project piloted an evidence evaluation framework of 44 questions that defines the scope of the review (i.e., disorder, genetic test, clinical scenario) and addresses the previously proposed components of evaluation: Analytic and Clinical validity, Clinical utility and associated Ethical, legal and social implications. The ACCE Project examined available evidence on five genetic testing applications, providing evidence summaries that could be used by others to formulate recommendations. Systematic reviews on genetic tests have also been conducted by other groups. Genetic tests tend to fit less well within “gold-standard” processes for systematic evidence review for several reasons. Many genetic disorders are uncommon or rare, making data collection difficult. Even greater challenges are presented by newly emerging genomic tests with potential for wider clinical use, such as genomic profiles that provide information on susceptibility for common complex disorders (e.g., diabetes, heart disease) or drug-related adverse events, and tests for disease prognosis. The actions or interventions that are warranted based on test results, and the outcomes of interest, are often not well defined. In addition, the underlying technologies are rapidly emerging, complex, and constantly evolving. Interpretation of test results is also complex, and may have implications for family members. Of most concern, the number and quality of studies are limited. Test applications are being proposed and marketed based on descriptive evidence and pathophysiologic reasoning, often lacking well-designed clinical trials or observational studies to establish validity and utility, but advocated by industry and patient interest groups.

THE EGAPP INITIATIVE
The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative is a multi-stakeholder process that translates genomic discoveries into testing applications that have potential to improve health care and usher in a new era of “personalized medicine.” For the last decade, questions have been raised about the appropriate evidentiary standards and regulatory oversight for this translation process. The US Preventive Services Task Force (USPSTF) was the first established national process to apply an evidence-based approach to the development of practice guidelines for genetic tests, focusing on BRC1/2 testing (to assess risk for heritable breast cancer) and on HFE testing for hereditary hemochromatosis. The Centers for Disease Control and Prevention-funded ACCE Project piloted an evidence evaluation framework of 44 questions that defines the scope of the review (i.e., disorder, genetic test, clinical scenario) and addresses the previously proposed components of evaluation: Analytic and Clinical validity, Clinical utility and associated Ethical, legal and social implications. The ACCE Project examined available evidence on five genetic testing applications, providing evidence summaries that could be used by others to formulate recommendations. Systematic reviews on genetic tests have also been conducted by other groups.

Prioritizing Genomic Applications for Action by Level of Evidence: A Horizon-Scanning Method

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Abstract

As evidence accumulates on the use of genomic tests and other health-related applications of genomic technologies, decision makers may increasingly seek support in identifying which applications have sufficiently robust evidence to suggest they might be considered for action. As an interim working process to provide such support, we developed a horizon-scanning method that assigns genomic applications to tiers defined by availability of synthesized evidence. We illustrate an application of the method to pharmacogenomics tests.
Scope of Genomics?

• 49 genetic “tests” on current Tier 1 list

• “Tier 1/Green genomic applications have a base of synthesized evidence that supports implementation in practice.”

• Referenced by those interested in genomics and population health
Scope of Genomics?

• Dominated by cancer pharmacogenomic testing – not screening!

• Cancer applications and PCPs
  – Family history for HBOC and breast cancer
  – Universal screening/cascade screening for Lynch syndrome (not really population screening)
Scope of Genomics?

• Also
  – 31 disorder newborn screening panel (pediatrics)
  – Family history of osteoporosis (women’s health)
  – Cascade screening for familial hyperlipidemia (internal medicine)
  – HLA B*1502 testing for carbamazepine (internal medicine)

• This is a fair diversity!
2) An evidence-oriented approach... to secondary findings.
For Immediate Release
Contact: Kathy Beal, MBA
Kbeal@acmg.net

ACMG Releases New Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing: Four Genes Added and One Removed in ACMG SF v2.0

BETHESDA, MD – NOVEMBER 17, 2016 | In order to promote standardized reporting of medically actionable information from clinical genomic sequencing, the American College of Medical Genetics and Genomics (ACMG) in 2013, published a minimum list of genes to be reported as secondary findings during exome or genome sequencing. The goal was to identify and manage risks for selected highly penetrant genetic disorders through established interventions aimed at preventing or significantly reducing morbidity and mortality. Subsequently, in 2014, the ACMG established the Secondary Findings Maintenance Working Group (SFWG) to develop a process for curating and updating the list of recommended genes periodically.

Now, the ACMG has released a highly-anticipated Updated Policy Statement, “Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing, 2016 Update: a Policy Statement of the American College of Medical Genetics and Genomics,” with four new genes added to the list of recommended secondary findings along with the elimination of one of those disorders from the list.
# Scope of Genomics

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### ACMG Statement

**Table 1** ACMG SF v2.0 genes and associated phenotypes recommended for return of secondary findings in clinical sequencing

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>MIM disorder</th>
<th>PMID Gene Review entry</th>
<th>Typical age of onset</th>
<th>Gene</th>
<th>MIM genes</th>
<th>Inheritance</th>
<th>Variants to report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast and ovarian cancer</td>
<td>604370</td>
<td>20001445</td>
<td>Adult</td>
<td>BRCA1</td>
<td>600185</td>
<td>AD</td>
<td>KP and EF</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>131625</td>
<td>20031488</td>
<td>Child/Adult</td>
<td>TP53</td>
<td>104760</td>
<td>AD</td>
<td>KP</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>175200</td>
<td>20031583</td>
<td>Child/Adult</td>
<td>STK11</td>
<td>600216</td>
<td>AD</td>
<td>KP and EF</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>129285</td>
<td>20031593</td>
<td>Adult</td>
<td>MLH1</td>
<td>600359</td>
<td>AD</td>
<td>KP</td>
</tr>
</tbody>
</table>

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http://www.nature.com/gim/journal/v19/n2/pdf/gim2016190a.pdf
Scope of Genomics

- Does not include PGX related variants
- Disease predisposition, some cancer
- Examples of genes added (4) and removed (1)
  - BMPR1A, SMAD4/juvenile polyposis
  - ATP7B/ Wilsons disease
  - OTC/ornithine transcarbamylase deficiency
  - MYLK/ familial thoracic aortic aneurysm
- Extensive, often esoteric waterfront....
Scope of Genomics?

3) The “Fully Monty”…
…screening with the “whole” genome in the well individual
Scope of Genomics?

Personalized genomic disease risk of volunteers

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Contributed by C. Thomas Caskey, August 27, 2013 (sent for review July 11, 2013)

Next-generation sequencing (NGS) is commonly used for researching the causes of genetic disorders. However, its usefulness in clinical practice for medical diagnosis is in early development. In this report, we demonstrate the value of NGS for genetic risk assessment and evaluate the limitations and barriers for the adoption of this technology into medical practice. We performed whole exome sequencing (WES) on 81 volunteers, and for each volunteer, we requested personal medical histories, constructed a three-generation pedigree, and required their participation in a comprehensive educational program. We limited our clinical reporting to disease risks based on only rare damaging mutations and known pathogenic variations in genes previously reported to be associated with human disorders. We identified 271 recessive risk alleles (214 genes), 126 dominant risk alleles (101 genes), and 3 X-recessive risk alleles (3 genes). We linked personal disease histories with causative disease genes in 18 volunteers. Furthermore, by incorporating family histories into our genetic analyses, we identified an additional five heritable diseases. Traditional genetic counseling and disease education were provided in verbal and written reports to all volunteers. Our report demonstrates that when genome results are carefully interpreted and integrated with an individual’s medical records and pedigree data, NGS is a valuable diagnostic tool for genetic disease risk.

Results

Categories of Variants to Report to Patients. Variants obtained from our workflow (described in Fig. 1) were reported using three categories. Our first variant category consists of variants identified in an individual where the alleles are found in Human Genome Mutation Database (HGMD) (13, 14) and labeled disease-causing mutations (DM). These alleles also were required to be rare [<1% allele frequency in 6,500 exomes from the National Heart, Lung, and Blood Institute (NHLBI) Exome Sequencing Project (15) and the 1,000 Genomes Project Genomes (16, 17)] and predicted to be damaging to protein function by two of three predictions algorithms [Polyphen 2.0 (18), Sift (19–24), and MutationTaster (25)] using Database of Human Non-synonymous SNVs and their functional predictions and annotations (dbNSFP) (26) as described in Fig. 2. The genome sequence data of each volunteer were reviewed and interpreted, taking into account personal medical history, a three-generation pedigree with family history of diseases, and bioinformatics analysis. The medical history of each volunteer in this cohort was rich with detail because each had a private physician used for annual examinations, and in some cases, disease therapy. Fig. 3 summarizes the results of our pipeline: we recruited 81 non-related volunteers and sequenced their genomic DNA using exome sequencing. We detected 65,882 unique nonsynonymous
Scope of Genomics?

Should Healthy People Have Their Exomes Sequenced?

With its announced launch of a whole-exome sequencing service for apparently healthy individuals, Ambry Genetics is the latest company to enter this growing market. But whether these services are useful for most people remains up for debate.

By Ruth Williams | March 24, 2017

http://www.the-scientist.com/?articles.view/articleNo/48974/title/Should-Healthy-People-Have-Their-Exomes-Sequenced-/)
Scope of Genomics?

- Multiple reputable companies now offering exome sequencing to healthy individuals
- Low cost ($500-$2K)
- Essentially available direct to consumer
- Minimal quality oversight
- NO standard approach to interpretation
- Really the Wild West…

http://www.the-scientist.com/?articles.view/articleNo/48974/title/Should-Healthy-People-Have-Their-Exomes-Sequenced-/
Roles?

- Active seeking of appropriate genomic data for health care?

- Passive/reactive use of genomic data for health care?

- Both?
Responsibilities?

• Selection of testing?
• Consent for testing?
• Interpretation of testing?
• Management?
• Stewardship of data?
• Communication of data?
The MedSeq Project: a randomized trial of integrating whole genome sequencing into clinical medicine

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Abstract

Background: Whole genome sequencing (WGS) is already being used in certain clinical and research settings, but its impact on patient well-being, health-care utilization, and clinical decision-making remains largely unstudied. It is also unknown how best to communicate sequencing results to physicians and patients to improve health. We describe the design of the MedSeq Project: the first randomized trials of WGS in clinical care.

Methods/Design: This pair of randomized controlled trials compares WGS to standard-of-care in two clinical contexts: (a) disease-specific genomic medicine in a cardiology/myopathy clinic and (b) general genomic medicine in primary care. We are recruiting 8 to 12 cardiologists, 8 to 12 primary care physicians, and approximately 200 of their patients. Patient participants in both the cardiology and primary care trials are randomly assigned to receive a family history assessment with or without WGS. Our laboratory delivers a genome report to physician participants that balances the needs to enhance understandability of genomic information and to convey its complexity. We provide an educational curriculum for physician participants and offer them a hotline to genetics professionals for guidance in interpreting and managing their patients' genome reports. Using varied data sources, including surveys, semi-structured interviews, and review of clinical data, we measure the attitudes, behaviors and outcomes of physician and patient participants at multiple time points before and after the disclosure of these results.

Discussion: The impact of emerging sequencing technologies on patient care is unclear. We have designed a process of interpreting WGS results and delivering them to physicians in a way that anticipates how we envision genomic medicine will evolve in the near future. That is, our WGS report provides clinically relevant information while communicating the complexity and uncertainty of WGS results to physicians and, through physicians, to their patients. This project will not only illuminate the impact of integrating genomic medicine into the clinical care of patients but also inform the design of future studies.

Trial registration: ClinicalTrials.gov identifier NCT01736566

Keywords: Whole genome sequencing, Genome report, Genomic medicine, Translational genomics, Primary care, Cardiomyopathy genetics.
Are Physicians Prepared for Whole Genome Sequencing? A Qualitative Analysis

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Abstract

**Background**—Although the integration of whole genome sequencing (WGS) into standard medical practice is rapidly becoming feasible, physicians may be unprepared to use it.
Roles/Responsibilities?

The Impact of Whole-Genome Sequencing on the Primary Care and Outcomes of Healthy Adult Patients

A Pilot Randomized Trial

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Background: Whole-genome sequencing (WGS) in asymptomatic adults might prevent disease but increase health care use without clinical value.

Objectives: To describe the effect on clinical care and outcomes of adding WGS to standardized family history assessment in primary care.

Design: Pilot randomized trial. (ClinicalTrials.gov: NCT 01736566)

Setting: Academic primary care practices.

Participants: 9 primary care physicians (PCPs) and 100 generally healthy patients recruited at ages 40 to 65 years.

Intervention: Patients were randomly assigned to receive a family history report alone (FH group) or in combination with an interactive WGS report (FH + WGS group), which included monogenic disease risk (MDR) results (associated with Mendelian disorders), carrier variants, pharmacogenomic associations, and polygenic risk estimates for cardiometabolic traits. Each patient met with his or her FH to discuss the report.

Measurements: Clinical outcomes and health care use through 6 months were obtained from medical records and audio-recorded discussions between PCPs and patients. Patients’ health behavior changes were surveyed 6 months after receiving results. A panel of clinician geneticsists rated the appropriateness of how PCPs managed MDR results.


data from the study

The benefits of clinical exome and genome sequencing are becoming clearer in the evaluation of highly heritable conditions and undiagnosed diseases (1, 2), in prenatal screening (3, 4), and in cancer treatment (5, 6). Many health care systems are moving toward more widespread adoption of clinical sequencing. Compared with simpler gene- or gene panel-based testing, whole-genome sequencing (WGS) brings additional complexity in terms of results. In clinical settings, it can deliver, ranging from monogenic disease risk (MDR) results indicating risk for Mendelian disorders to common disease risk for common variation in polygenic conditions. Sequencing is still predominant in the province of genetics specialists, but its expansion in this era of limited health care resources, including access to genetics professionals, evokes concern. The main considerations are whether non-geneticist physicians and primary care physicians (PCPs) can manage genomic information appropriately (7-9) and the degree to which clinicians integrate genomics into early disease detection and prevention or leads to anxiety and unnecessary and costly follow-up (10, 11).

Although the risk-benefit ratio of sequencing is probably favorable in specific clinical contexts, the risks and costs of sequencing might outweigh its benefits for individual healthy persons. To examine this balance, we developed a process to perform clinical WGS, interpret the results, and develop a WGS report that non-geneticist physicians could use, and measure downstream clinical outcomes. To provide early empirical evidence about the risks and benefits of integrating sequencing.

See also:
Editorial comment ........................................... 204
Summary for Patients ....................................... 1-20
Web-Only Supplement

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*For members of the MedSeq Project, see the Appendix (available at Annals.org).
What is next?

The cart is pretty far out in front of the horse…
Emerging models

Moving the genome into the clinic

The Clinical Sequencing Exploratory Research (CSER) Consortium, a national multi-site research program funded jointly by the National Human Genome Research Institute (NHGRI) and National Cancer Institute (NCI), conducts multidimensional, translational research to evaluate the integration of genome and exome sequencing into clinical care. Comprising of over 300 clinicians, scientists, ethicists, bioinformaticians, economists, and legal scholars, and recruiting over 5000 patients across diverse clinical indications, backgrounds, and age groups, CSER is well positioned to study the impacts and effectiveness of using genomic sequencing in clinical care. Through this expertise and research, CSER has and continues to develop and share innovations and best practices in areas such as variant classification, return of results, additional (incidental) findings, informed consent, and ethical, legal and social implications of sequencing.

CSER Tools for Genomic Medicine

CSER developed tools and resources to support the genomic medicine process.

Achievements [+]
The future of health begins with All of Us

The All of Us Research Program is a historic effort to gather data from one million or more people living in the United States to accelerate research and improve health. By taking into account individual differences in lifestyle, environment, and biology, researchers will uncover paths toward delivering precision medicine.

https://allofus.nih.gov/
Emerging models

https://www.genomicsengland.co.uk//
Emerging models

Independent report

Chief Medical Officer annual report
2016: Generation Genome

From: Department of Health
Published: 4 July 2017
Last updated: 20 July 2017, see all updates

Professor Dame Sally Davies's eighth independent report to government as CMO looks at how genomics can improve health and prevent ill-health.

Documents

Annual report of the Chief Medical Officer
2016: Generation Genome

PDF, 11.5MB, 256 pages
This file may not be suitable for users of assistive technology. Request an accessible format.

Emerging models

Emerging models
Augusta’s cancer center hosts genomics research initiative

The program, directed by two headed from the Jackson Laboratory, will allow oncologists throughout the state to share technology, information.

BY BETTY ADAMS STAFF WRITER

Emerging models

• No single program will have the power to fully investigate the consequences of rare variations.
• There is no consensus approach for interpretation and action.
• There are no shared outcomes and metrics across US programs.
Emerging models

http://www.nationalacademies.org/hmd/Activities/Research/GenomicBasedResearch.aspx
Three take home points

• Integration of genomics into primary care practice has largely been explored through the lens of a few tests at a time. This is a problem!

• The net value of genomics in primary care remains undefined. Overdiagnosis > underdiagnosis.

• What is happening at your institution? The genomics community needs you as a constructive partner in getting it right!