Northwestern Medicine®
Feinberg School of Medicine

Implementation of Public Health Genomics & Applications to Oral Health

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Today's Learning Objectives

- Name three genetic conditions that are relevant to oral health and public health genomics
- Describe a public health approach to determine if a genetic test is ready for implementation at the clinical and/or population level
- List two available public health genomics resources that are useful to dental public health professionals

Vision for Public Health Genomics

"Genomics will be to the 21st century what infectious disease was to the 20th century…

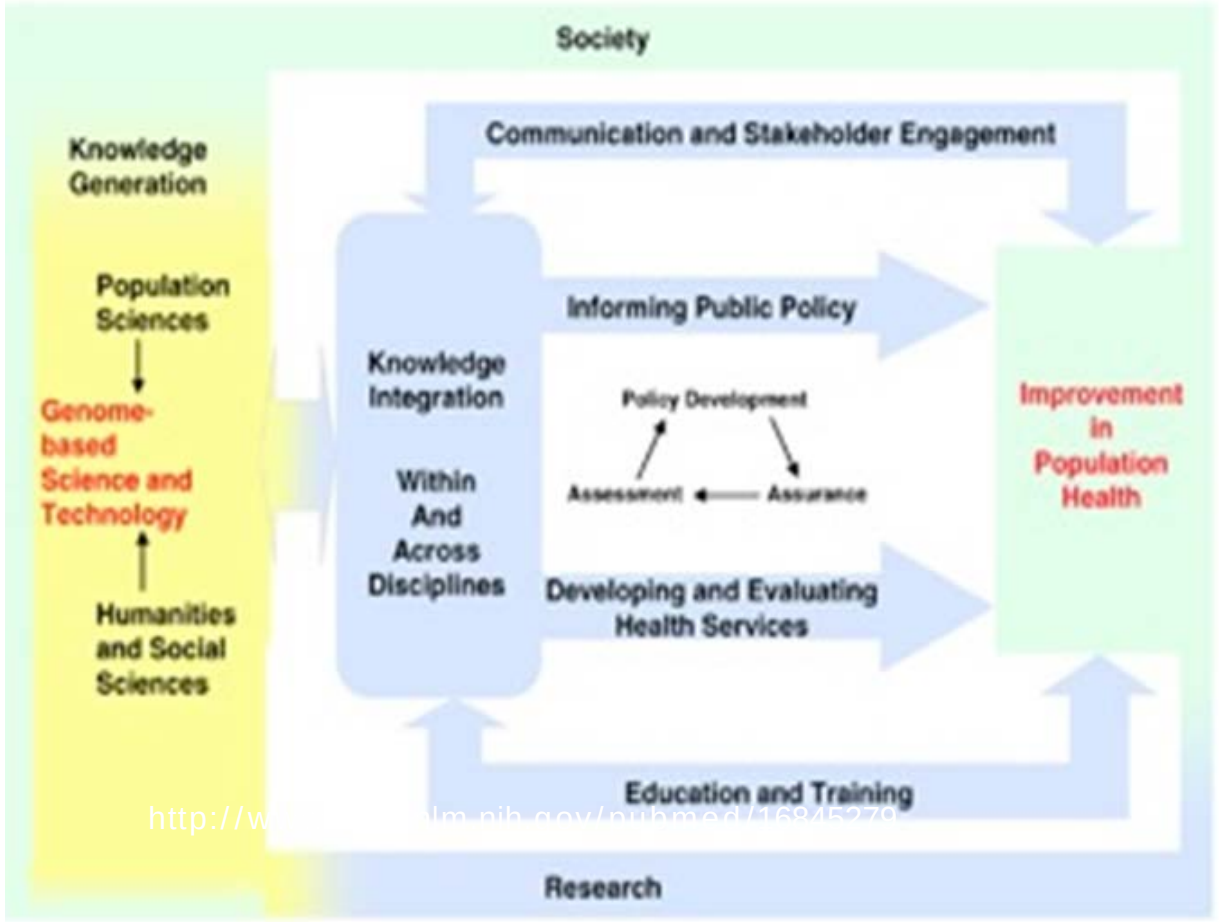
Genomics should be considered in every facet of public health: infectious disease, chronic disease, occupational health, environmental health, in addition to maternal and child health"

…and importantly dental public health!

Gerard et al. Journal Law, Medicine , Ethics **2002**; vol 30(suppl):173-176

What is Public Health Genomics?

- A **multidisciplinary** field concerned with the **effective and responsible** translation of genome-based knowledge and technologies to improve population health
  - Bellagio Statement, 2006



Public Health Genomics: Collaboration Among Multiple Stakeholders including Dental Public Health Professionals

"...no important health problem will be solved by clinical care alone, or research alone, or by public health alone- But rather by all public and private sectors working together"

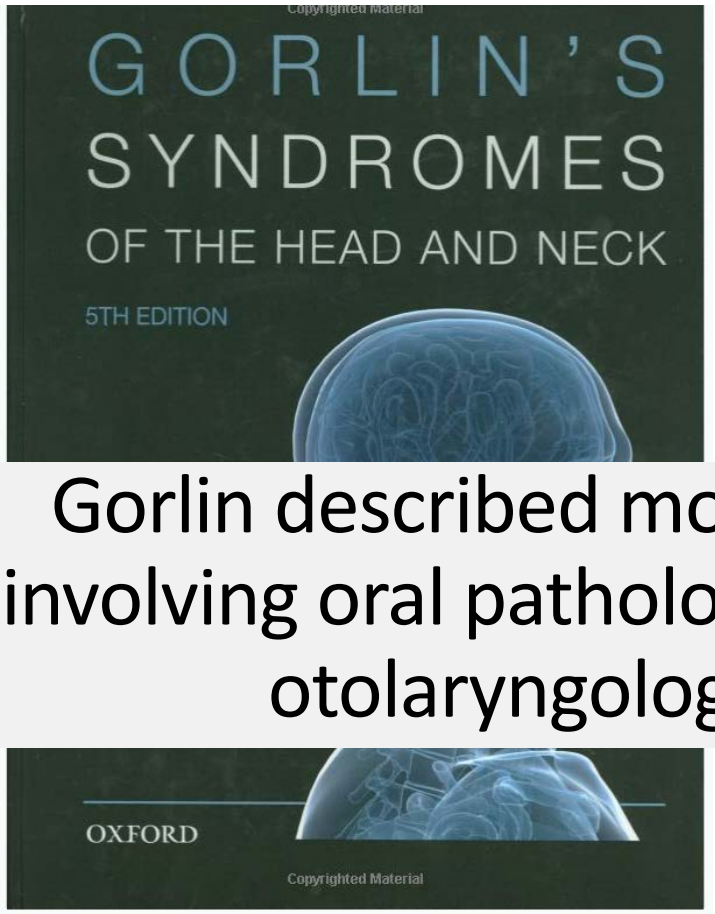
JS Marks. Managed Care 2005;14:p11
Supplement on "The Future of Public Health"

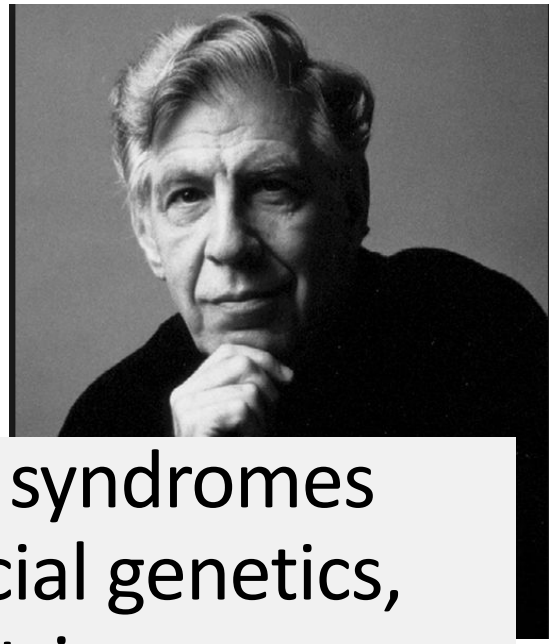
Multitude of Genetic Conditions with Dental Implications

- Of the approximately 5,500 known human genetic disorders,
  - 30-40% are important to the dental community
  - More than 700 are craniofacial disorders
  - More than 200 genes involved in the embryogenic development, morphogenesis and differentiation of the teeth
  - **Chromosome abnormalities, genetic syndromes, and non-syndromic isolated and multifactorial genetic factors**
  - However, only one dental school requires one semester of molecular biology or genetics for admission (Hart & Hart, 2016)
  - Dental schools encouraged to include human genetics as a formal course in curricula

Hart PS & Hart TC, Molecular Genetics and Genomic Medicine, 2016, 123-125

Robert (Bob) Gorlin, DDS, MS, 1923-2006





Gorlin described more than 100 syndromes involving oral pathology, craniofacial genetics, otolaryngology and obstetrics

"In human genetics, we think Bob belongs to us, but the dentists, the pathologists, the dermatologists, the oncologists, the reconstructive surgeons, and the craniofacial specialists all think he belongs to them too." - Judy Hall

What is Genetic Counseling?

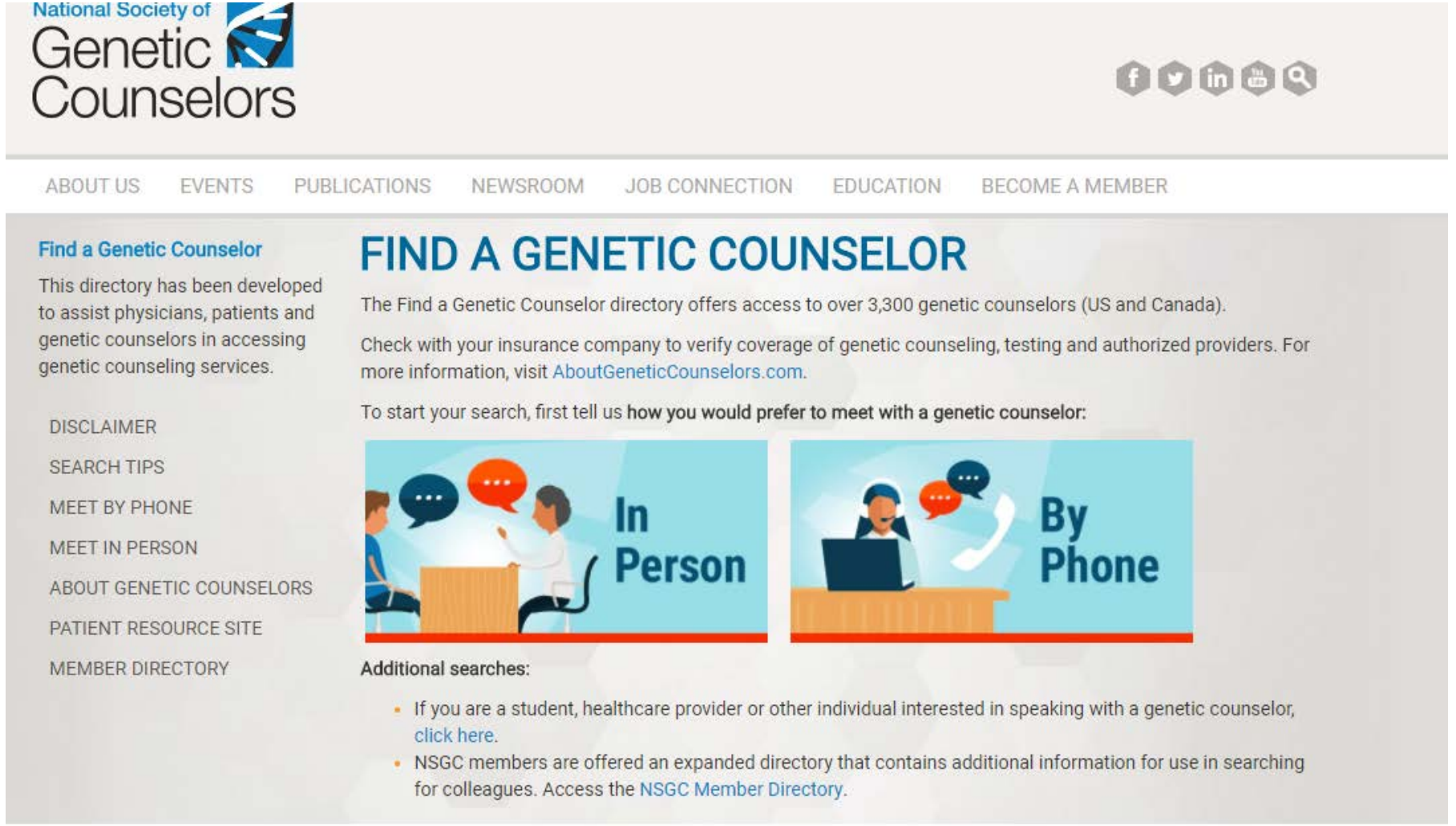
- Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following:
  - Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
  - Education about inheritance, testing, management, prevention, resources and research.
  - Counseling to promote informed choices and adaptation to the risk or condition.

Resta et al, J Genet Counseling, 2006 Apr;15(2):77-83

Genetic Counseling Specialties

Historically	Adult	Treatment
• Prenatal • Pediatrics	• Cancer • Neurogenetic • Cardiology • Psychiatry • Endocrine • General	• Somatic sequencing/with or without germline to dictate treatment • Germline sequencing to dictate treatment • Pharmacogenomics

- Industry
- Laboratory utilization
- Research
- Public Health



https://www.nsgc.org/page/find-a-genetic-counselor

National Society of Genetic Counselors (NSGC) Vision

"Integrating genetics and genomics to improve health for all"

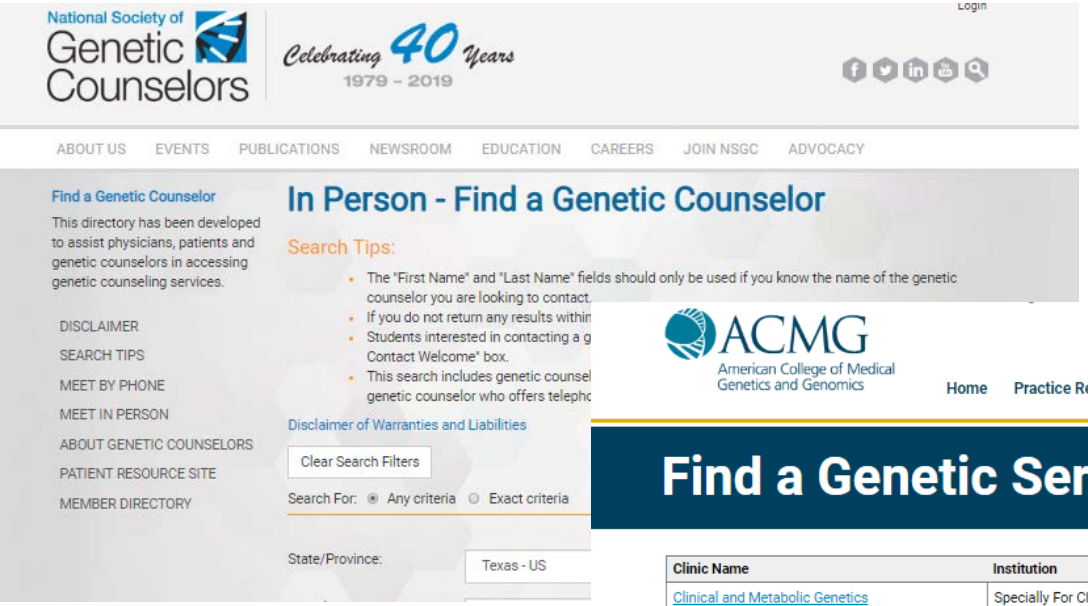
http://www.nsgc.org/page/about-nsgc

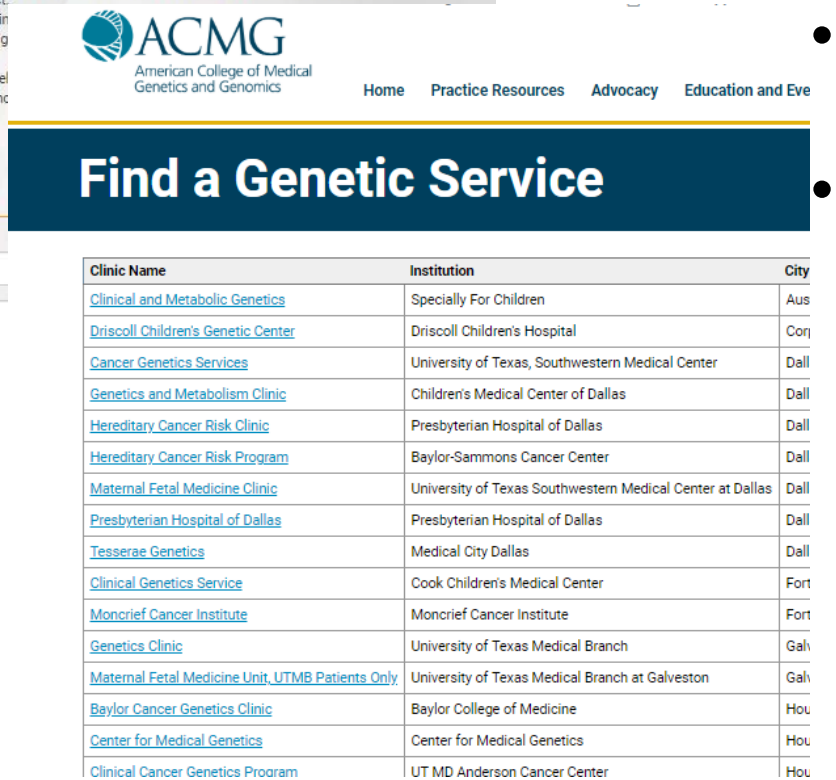
….For All!

- ~324 million people of the United States
- Ensure access to all regardless of race, gender, income, geography, and ability to pay
- Only ~4,000 certified genetic counselors in US (2017)
- Need to engage dental community!
  - 61 dentists practicing per 100,000 US population (2017)
  - In Texas, ~10,451 licensed general dentists, 12,971 licensed dental hygienists, 35,784 registered dental assistants!

http://www.aha.org/research/rc/stat-studies/fast-facts.shtm
https://www.ada.org/en/science-research/health-policy-institute/dental-statistics/workforce; file:///C:/Users/ddk9013/Downloads/2019-20StateHealthPlan%20(1).pdf

Please Consider Connecting with Your Local Genetics Clinic or Genetic Counselor!





- Consider developing partnership between dental public health and genetics professionals at the local level
- Consider contacting your local genetics clinic
- In Texas, there are ~30 genetic clinics and ~100 genetic counselors; typically located in academic centers in larger cities
  - Some have outreach clinics and services available in rural and underserved areas in Texas

https://www.acmg.net/ACMG/Genetic_Services_Directory_Search.aspx

Referrals to Genetics Services Based on Dental Findings

- Dental public health professionals can help to assure access and appropriate health management of individuals with genetic conditions
- Consider contacting local genetic services to discuss possible appropriate referrals
- Steps to consider for routine genetics evaluation for dental health professionals:
  - Collect and evaluate family and medical history
  - Consider unusual dental findings and associations with other conditions (e.g., oligodontia and colon cancer, enamel defects and kidney disease, microdontia and deafness)
  - Consider routinely collecting genetic conditions with potential oral health implications
  - Consider referral to genetic counselor or other specialists when appropriate
  - Include dental health professionals as part of personalized medicine team/multidisciplinary genetic specialty clinic

My Family Health Portrait

A tool from the Surgeon General

Language English

Using My Family Health Portrait you can:

- Enter your family health history.
- Learn about your risk for conditions that can run in families.
- Print your family health history to share with family or your health care provider.
- Save your family health history so you can update it over time.

Talking with your health care provider about your family health history can help you stay healthy!

Learn more about My Family Health Portrait

Create a Family Health History

Use a Saved History

https://phgkb.cdc.gov/FHH/html/index.html

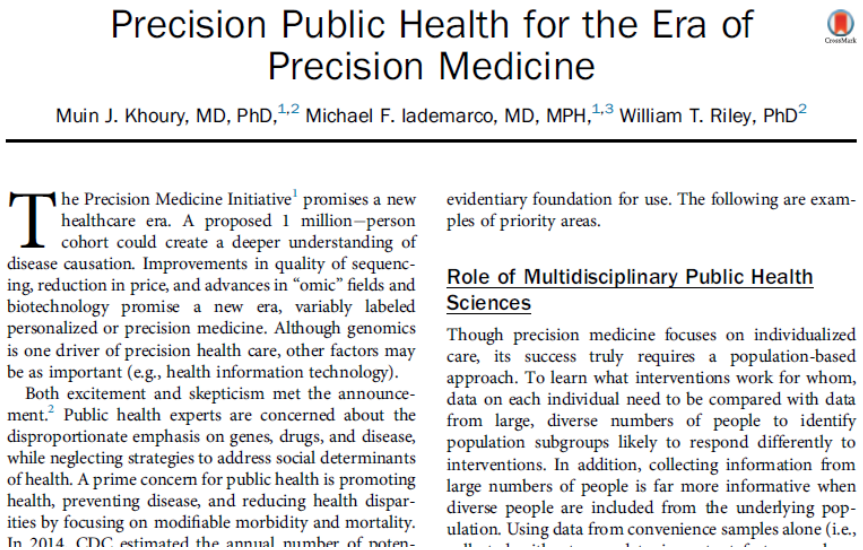
Precision Public Health

- Rapidly evolving field; no uniform definition
  - Term first used in 2016

- Recent proposed definitions:
  - **The application and combination of new and existing technologies, which more precisely describe and analyze individuals and their environment over the life course, to tailor preventive interventions for at-risk groups and improve the overall health of the population**

  - **“Right intervention at the right time, every time to the right population”**

- Emphasizes interventions; data and informatics



Precision Public Health for the Era of Precision Medicine

Muin J. Khoury, MD, PhD,[1,2] Michael F. Iademarco, MD, MPH,[1,3] William T. Riley, PhD[2]

The Precision Medicine Initiative[1] promises a new healthcare era. A proposed 1 million—person cohort could create a deeper understanding of disease causation. Improvements in quality of sequencing, reduction in price, and advances in “omic” fields and biotechnology promise a new era, variably labeled personalized or precision medicine. Although genomics is one driver of precision health care, other factors may be as important (e.g., health information technology).

Both excitement and skepticism met the announcement.[2] Public health experts are concerned about the disproportionate emphasis on genes, drugs, and disease, while neglecting strategies to address social determinants of health. A prime concern for public health is promoting health, preventing disease, and reducing health disparities by focusing on modifiable morbidity and mortality. In 2014, CDC estimated the annual number of poten-

evidentiary foundation for use. The following are examples of priority areas.

Role of Multidisciplinary Public Health Sciences

Though precision medicine focuses on individualized care, its success truly requires a population-based approach. To learn what interventions work for whom, data on each individual need to be compared with data from large, diverse numbers of people to identify population subgroups likely to respond differently to interventions. In addition, collecting information from large numbers of people is far more informative when diverse people are included from the underlying population. Using data from convenience samples alone (i.e.,

Weeramantrhi et al, Frontiers in Public Health, 2018
Khoury et al, AJPM, 2016

The traditional population health perspective on screening & prevention: one size fits all

The precision medicine approach to screening & prevention: risk-based paradigm

General population risk

Family history

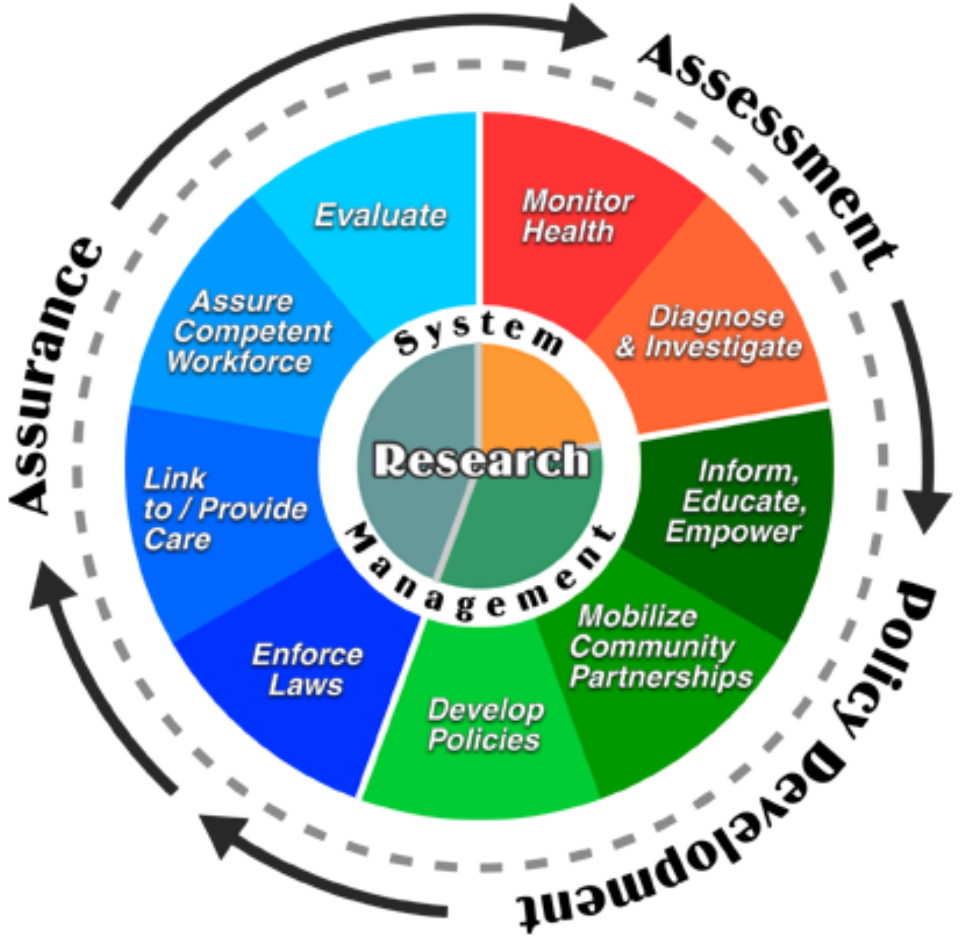
High risk family history

Mutation carrier

Precision Public Health
Can We Conduct Public Health Functions With More "Precision"?

The 3 Core Public Health Functions

- **Assessment**
  - More "precision" in measuring population health problems
- **Policy Development**
  - Developing the right intervention for the right population
- **Assurance**
  - More "precision" in delivering interventions & addressing health disparities

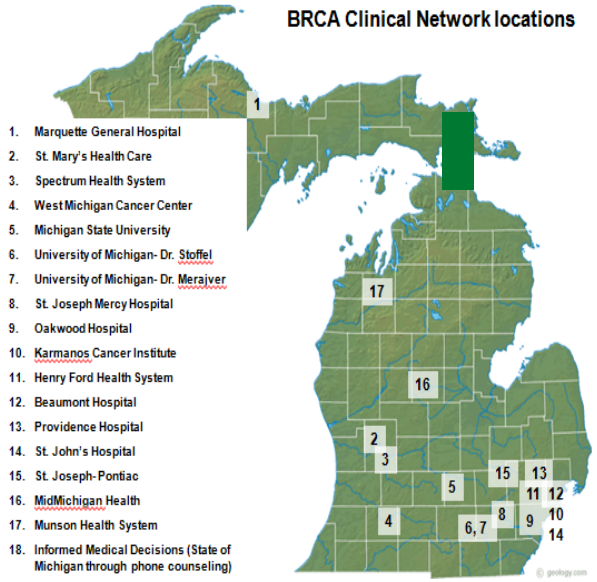


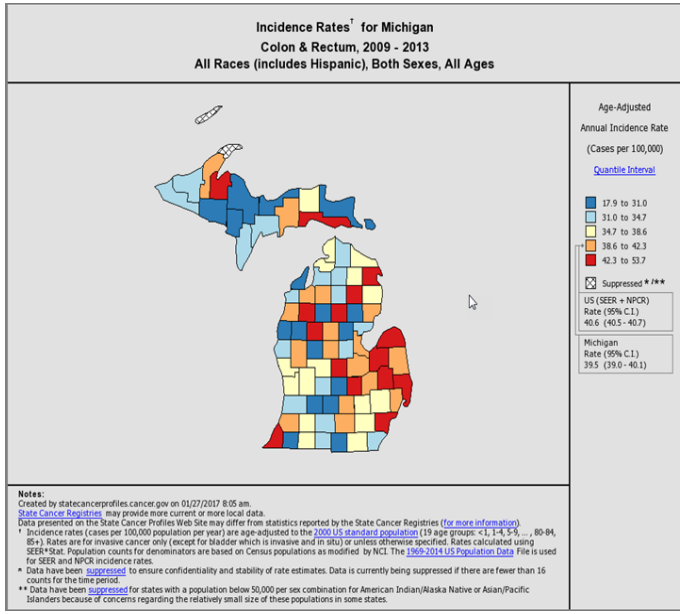
An Example from Michigan: Building Relationships with Primary Care Health Networks in Michigan Underserved Geographic Areas

Locations of Michigan cancer genetic clinics with board-certified genetic professionals (*BRCA* Clinical Network)

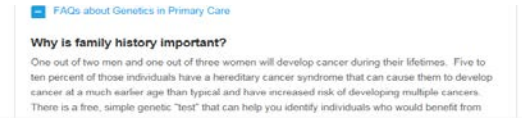
Counties with higher age-adjusted incidence and mortality of cancers of interest (State Cancer Registry)

Primary care provider engagement and education in underserved counties with higher incidence/mortality





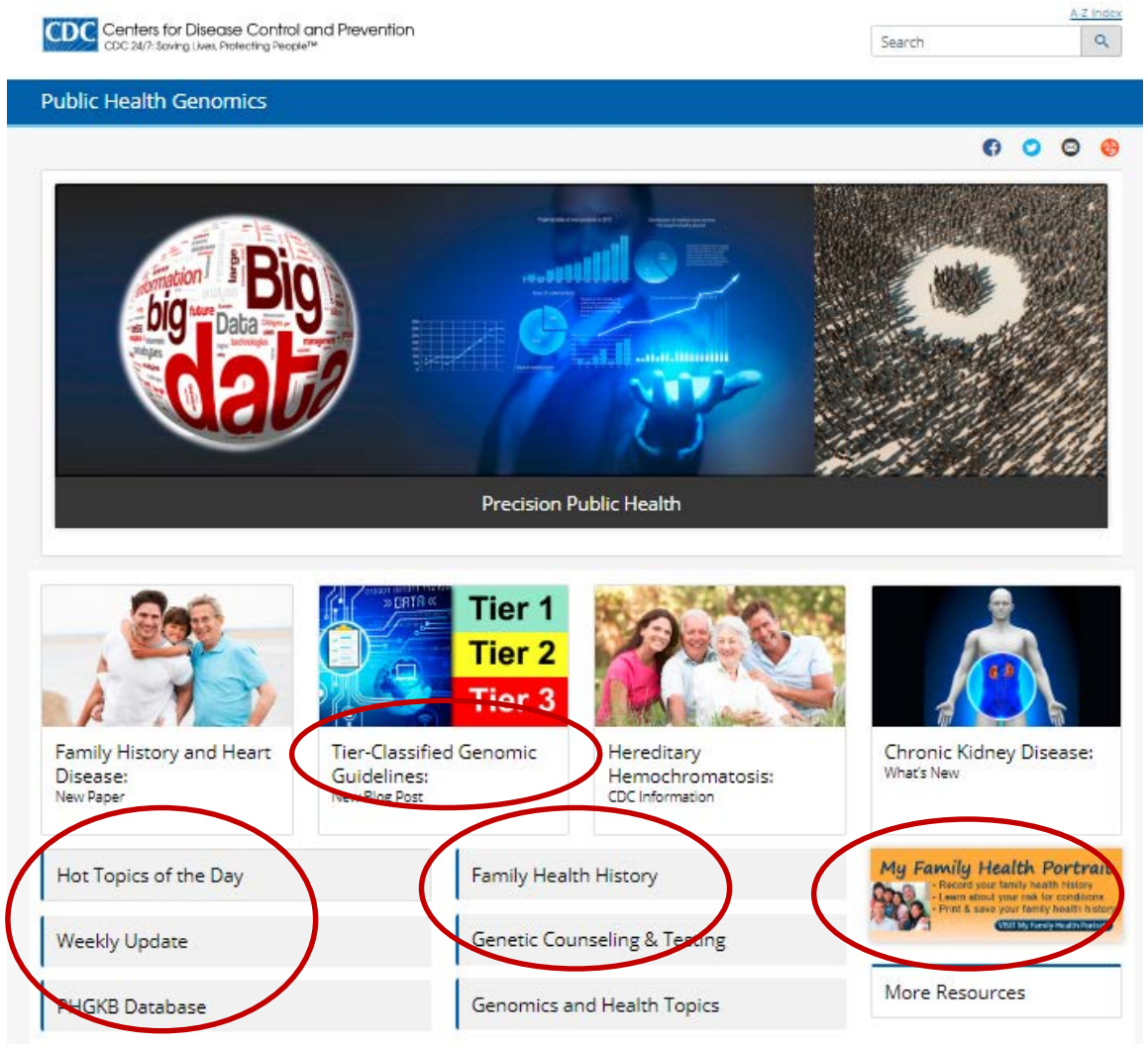
Consider engagement and education of dental public health professionals in underserved counties in Texas with higher incidence/mortality of cancers of interest?



https://statecancerprofiles.cancer.gov/map/map.withimage.php?26&001&020&00&0&01&0&1&5&0#results

http://www.jaxge.org/workshops/

CDC Office of Public Health Genomics



http://www.cdc.gov/genomics/

Increase in Number of Genetic Tests:

How many have a sufficient evidence for their use in clinical or public health practice?

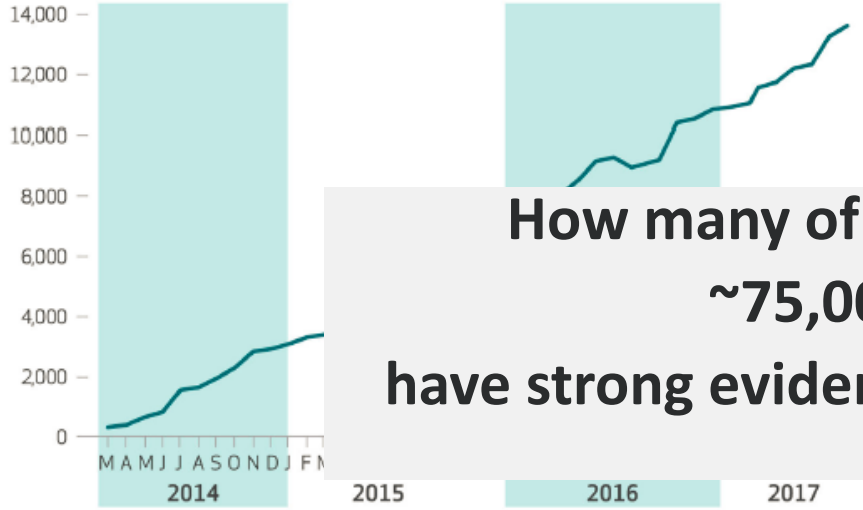


Exhibit 1.
Cumulative number of new genetic tests on the market, by month, March 2014–August 2017
SOURCE Authors' analysis of data from the Concert Genetics test catalog database.

How many of the currently available
~75,000 genetic tests
have strong evidence for their use in practice?

- Recent study examined test availability and spending for genetic tests, 2014-2017
- ~75,000 genetic tests on the market with **e market daily**

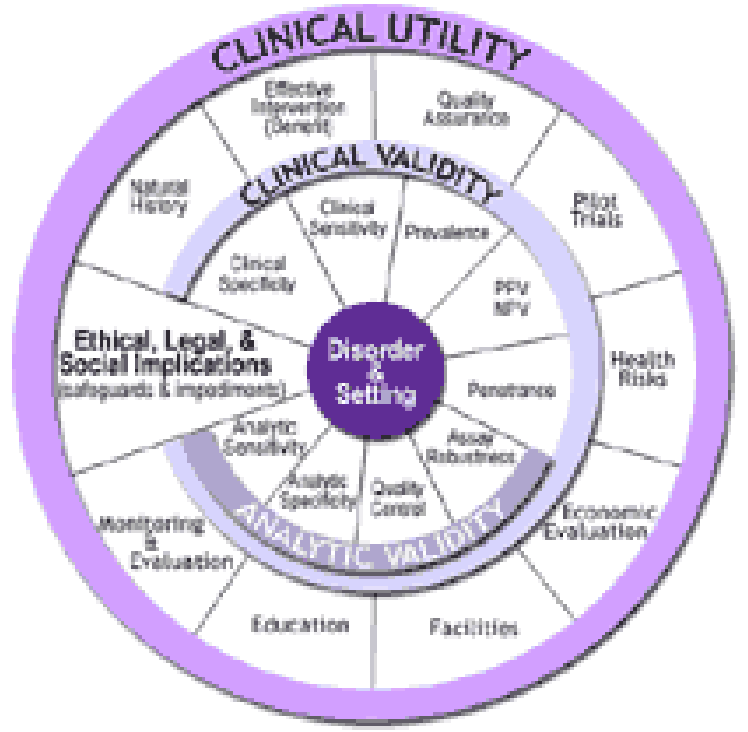
2014-2017

- Highest percentage of spending by clinical domain was on prenatal tests and second highest on hereditary cancers

Phillips et al; Health Aff. May 2018; 37(5): 710-717

Key Questions to Consider about Genetic Tests

- ✓ How valid and reliable are the genomic tests/services?(**analytic validity**)
- ✓ How well does the test/service predict outcomes? (**clinical validity**)
- ✓ What are the benefits and harms when the test/service is used to influence patient management? (**clinical utility**)
- ✓ How should the medical community, public health, policy makers respond? (**ethical, legal, social issues**)



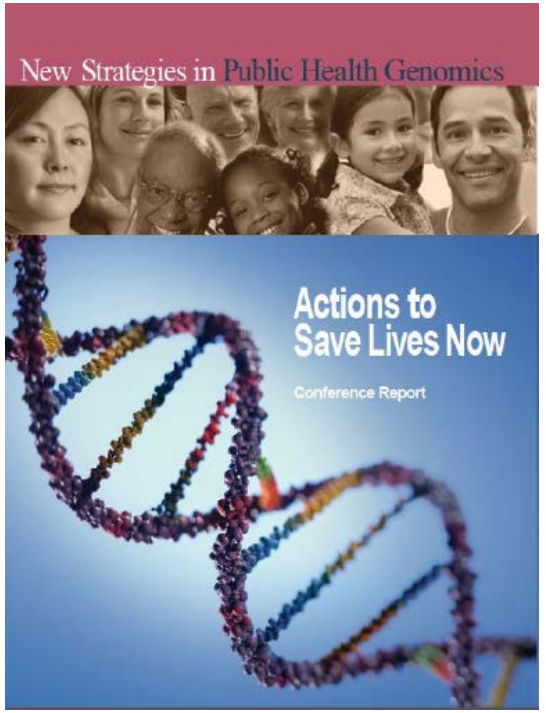
https://www.cdc.gov/genomics/gtesting/acce/

Small Number of Tests Known to Save Lives

- Tier 1 Tests per CDC Office of Public Health Genomics
  - Proven analytic validity, clinical validity and clinical utility
  - Can save lives!
  - Often underused in clinical practice

- ~80 genomic tests supported by evidence for use in practice
  - Most are cancer-related tests

- Many intended uses include
  - Diagnosis
  - Prognosis
  - Risk prediction to inform prevention
  - Treatment, including choice of medication and dosage
  - Screening



Centers for Disease Control and Prevention. genomicsforum.org/editoruploads/ActionstoSaveLivesNowReport.pdf

Three-Tier Classification of Recommendations on Genomic Applications

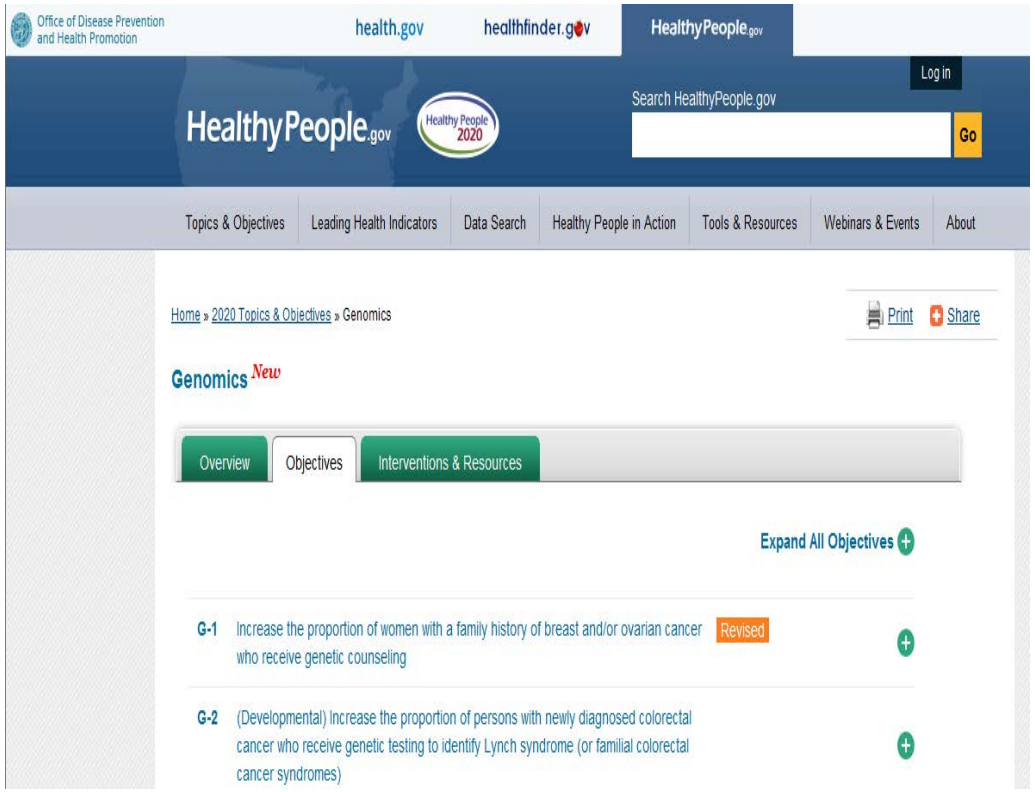
- **Tier 1: Ready for implementation**
  - Demonstrated analytic validity, clinical validity, clinical utility and evidence-based recommendations
  - Health professionals: encourage use; can save lives!
    - Examples: *BRCA (Grade B),* Lynch syndrome, familial hypercholesterolemia, hypertrophic cardiomyopathy, newborn screening

- **Tier 2: Informed decision making**
  - Adequate information on analytic and clinical validity, promising but not definitive information on clinical utility; no evidence-based guidelines recommending clinical use
    - Health professionals: provide information for shared decision making
      - Examples: Several different pharmacogenomics tests to treat mental illness

- **Tier 3: Discourage use**
  - No or little information on analytic, clinical validity or clinical utility; or evidence of harm
  - **With exception of newborn screening, there are not any genetic tests that should yet be offered to the entire population**
  - Health professionals: discourage use; may be considered for research in select instances; reduce potential harms and save unnecessary healthcare costs
    - Examples: *BRCA (Grade D),* Population screening for hereditary hemochromatosis

Khoury MJ et al. Am J Prev Med 2011;
Bowen MS et al Public Health Genomics 2012

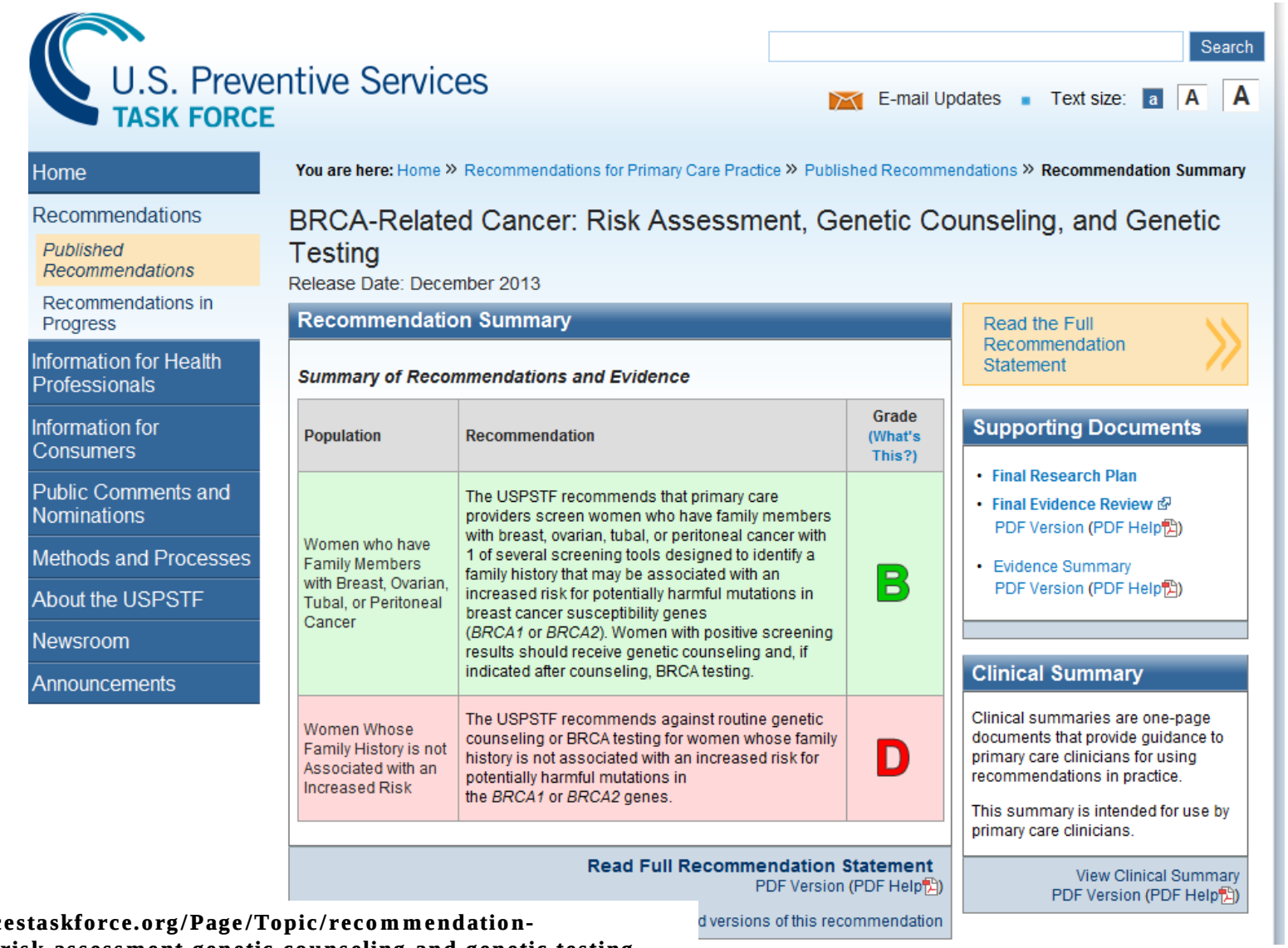
Healthy People 2020 (HP 2020) Cancer Genomics Objectives



http://www.healthypeople.gov/2020/topics-objectives/topic/genomics/objectives

- HP 2020 marks first time for genomics objectives; likely to be included in HP2030
- **Increase the proportion of women with a family history of breast and/or ovarian cancer who receive genetic counseling**
- **Increase the proportion of persons with newly diagnosed colorectal cancer who receive genetic testing to identify Lynch syndrome (or familial colorectal cancer syndromes)**
- Estimated that up to **2 million** in US have one of these conditions and vast majority are undiagnosed!
- CDC has funded multiple projects to address these HP2020 objectives
  - To my knowledge, none have involved dental health providers
  - **Let's consider adding YOU to these efforts!**

Example of Tier 1 and Tier 3: 2013 USPSTF *BRCA*-Related Cancer Recommendation (updated from 2005)



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BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing

Release Date: December 2013

Recommendation Summary

Summary of Recommendations and Evidence

Population	Recommendation	Grade (What's This?)
Women who have Family Members with Breast, Ovarian, Tubal, or Peritoneal Cancer	The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with 1 of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (*BRCA1* or *BRCA2*). Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing.	B
Women Whose Family History is not Associated with an Increased Risk	The USPSTF recommends against routine genetic counseling or BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes.	D

Read Full Recommendation Statement
PDF Version (PDF Help)

d versions of this recommendation

Read the Full Recommendation Statement

Supporting Documents

- Final Research Plan
- Final Evidence Review
  PDF Version (PDF Help)
- Evidence Summary
  PDF Version (PDF Help)

Clinical Summary

Clinical summaries are one-page documents that provide guidance to primary care clinicians for using recommendations in practice.

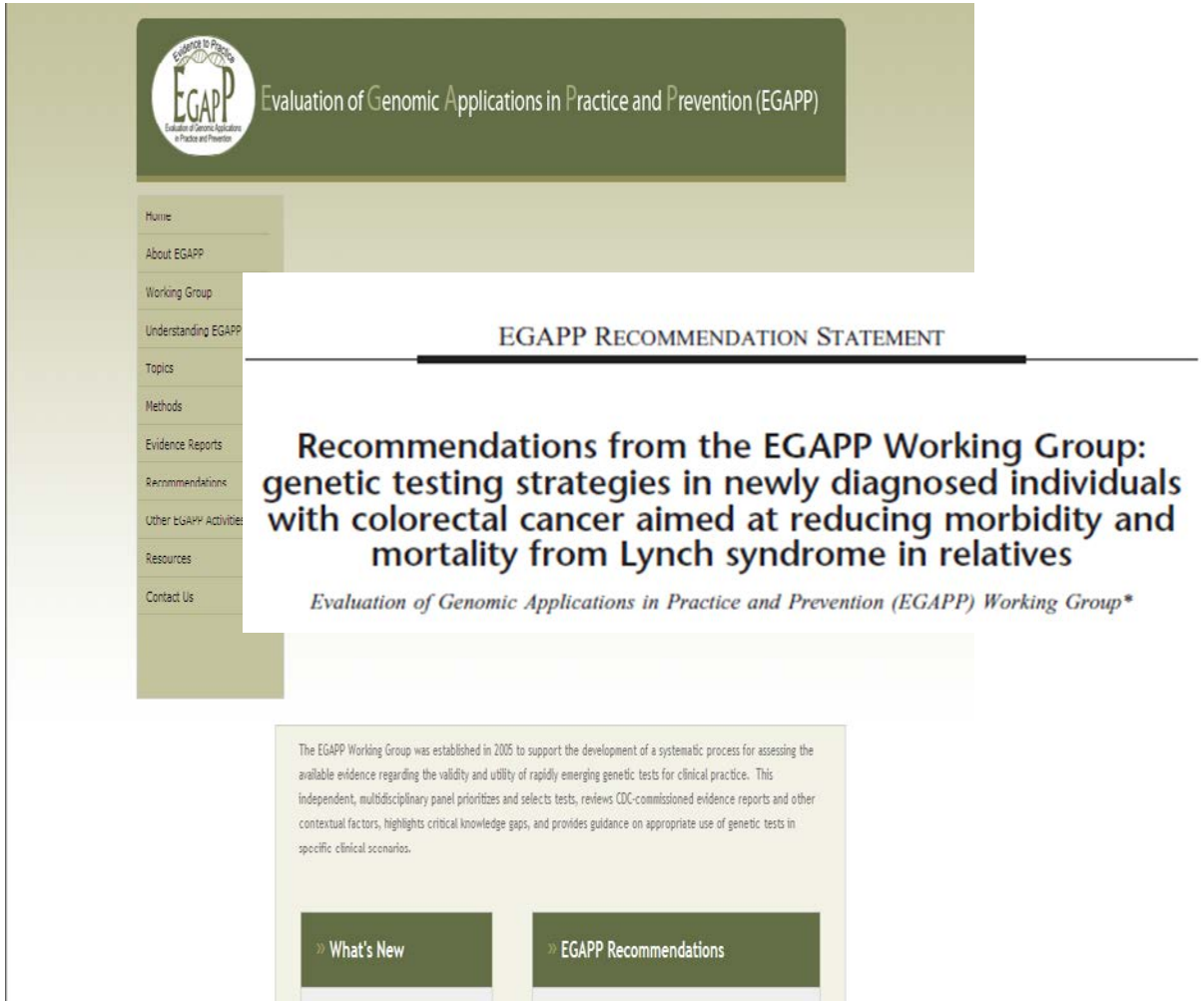
This summary is intended for use by primary care clinicians.

View Clinical Summary
PDF Version (PDF Help)

http://www.uspreventiveservicestaskforce.org/Page/Topic/recommendation-summary/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing

EGAPP Recommendation on Genetic Testing for Lynch Syndrome

- Sufficient evidence to offer counseling & genetic testing for Lynch syndrome to patients newly diagnosed with colorectal cancer to reduce morbidity & mortality in relatives
- Relatives of patients who test positive for Lynch could be offered counseling, testing &, if positive, increased colonoscopy
- Evidence of benefit to the patient's relatives



Gen Med 2009;11:35-41&42-65

Three-Tier Classification

Green

- FDA label requires use of test to inform choice or dose of a drug
- CMS covers testing
- Clinical practice guidelines based on systematic review supports testing

Yellow

- FDA label mentiones biomarkers*
- CMS coverage with evidence development
- Clinical practice guideline, not based on systematic review, supports use of test
- Clinical practice guideline finds insufficient evidence but does not discourage use of test
- Systematic review, without clinical practice guideline, supports use of test
- Systematic review finds insufficient evidence but does not discourage use of test
- Clincial practice guideline recommends dosage adjustment, but does not address testing

Red

- FDA label cautions against use
- CMS decision against coverage
- Clincial practice guideline recommends against use of test
- Clinical practice guideline finds insufficient evidence and discourages use of test
- Systematic review recommends against use
- Systematic review finds insufficient evidence and discourages use
- Evidence available only from published studies without systematic reviews, clinical practice guidelines, FDA label or CMS labels coverage decision

*Can be reassigned to Green of Red of one or more conditions in these categories apply

- https://phgkb.cdc.gov/PHGKB/topicStartPage.action

Genomics Translation Highway: Discovery to Implementation of Genomics Applications for Population Health Impact

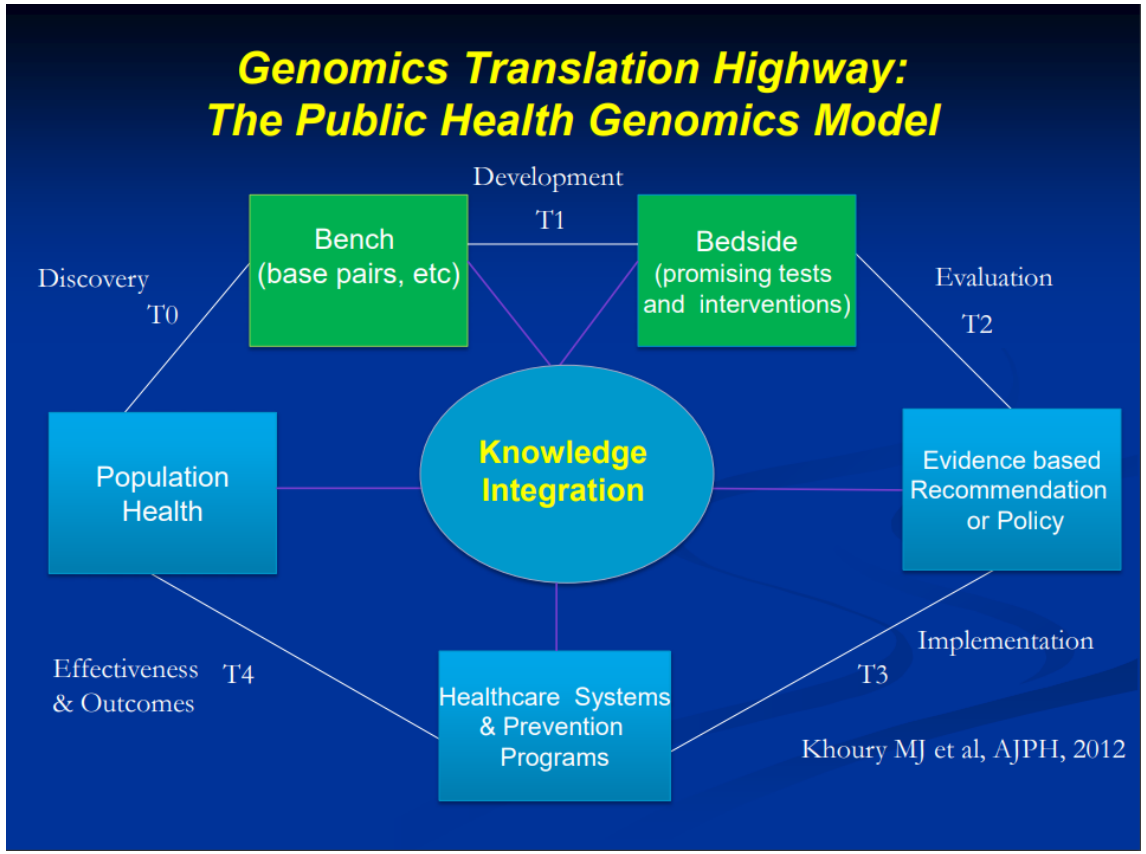


Table 1: The continuum of translational research in cancer genetics: type

Translation research phase	Notation	Examples of types of research
T0	Gene and other discoveries	GWASs, candidate gene studies
T1	Discovery to candidate health application	Phase I and II clinical trials; observational studies to characterize genes and gene–environment interaction; pharmacogenomics
T2	Health application to evidence-based practice guidelines	Phase III clinical trials; observational studies; evidence synthesis and guidelines development
T3	Practice guidelines to health practice	Dissemination research; implementation research; diffusion research; phase IV clinical trials
T4	Practice to population health impact	Outcomes research; population monitoring of morbidity, mortality, benefits, and risks

GWAS, genome-wide association study.

Periodontal Disease: Complex Multifactorial Disease

"In the genomic era, it is not human genes alone but the interplay of multiple genes, epigenetics, the microbial genome and their interactions with oral hygiene, diet, exercise, behaviors and substance abuses that influence the type and severity of periodontal diseases."

- Harold Slavkin, DDS

Journal of Public Health Dentistry, 2018

Example of Importance of Dental Public Health Genomics Framework: Interleukin-1 & Preventive Dental Care

RESEARCH REPORTS
Clinical

W.V. Giannobile[1,2*], T.M. Braun[1,3], A.K. Caplis[1], L. Doucette-Stamm[4], G.W. Duff[5], and K.S. Kornman[4]

Patient Stratification for Preventive Care in Dentistry

[1]Michigan Center for Oral Health Research, University of Michigan School of Dentistry, Ann Arbor, MI, USA; [2]Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry, Ann Arbor, MI, USA; [3]Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI, USA; [4]Interleukin Genetics, Inc., Waltham, MA, USA; and [5]University of Sheffield, Division of Genomic Medicine, Sheffield, UK; *corresponding author, william.giannobile@umich.edu

J Dent Res 92(8):694-701, 2013

ABSTRACT

Prevention reduces tooth loss, but little evidence supports biannual preventive care for all adults. We used risk-based approaches to test tooth loss association with 1 *vs.* 2 annual preventive visits in high-risk (HiR) and low-risk (LoR) patients. Insurance claims for 16 years for 5,117 adults were evaluated retrospectively for tooth extraction events. Patients were classified as HiR for progressive periodontitis if they had ≥ 1 of the risk factors (RFs) smoking, diabetes, interleukin-1 genotype; or as LoR if no RFs. LoR event rates were 13.8% and 16.4% for 2 or 1 annual preventive visits (absolute risk reduction, 2.6%; 95%CI, 0.5% to 5.8%; $p = .092$). HiR event rates were 16.9% and 22.1% for 2 and 1 preventive visits (absolute risk reduction, 5.2%; 95%CI, 1.8% to 8.4%; $p = .002$). Increasing RFs increased events ($p < .001$). Oral health care costs were not increased by any single RF, regardless of prevention frequency ($p > .41$), but multiple RFs increased costs *vs.* no ($p < .001$) or 1 RF ($p = .001$). For LoR individuals, the association between preventive dental visits and tooth loss was not significantly different whether the frequency was once or twice annually. A personalized medicine approach combining gene biomarkers with conventional risk factors to stratify populations may be useful in resource allocation for preventive dentistry (ClinicalTrials.gov, NCT01584479).

KEY WORDS: comparative effectiveness research, personalized medicine, periodontal disease, interleukin polymorphisms, oral health, health care delivery.

DOI: 10.1177/0022034513492336

INTRODUCTION

Health care costs in many countries appear unsustainable (Keehan *et al.*, 2011), and a substantial proportion of those costs may arise from unnecessary services and missed opportunities to prevent chronic diseases (Yong and Olsen, 2010).

Tooth loss in adults is primarily attributable to periodontitis (PD) and dental caries (Murray *et al.*, 1996; Ong *et al.*, 1996; Chrysanthakopoulos, 2011; Mai *et al.*, 2013). Periodontitis is a common chronic inflammatory disease affecting 47% in the U.S., with 8.5% having severe disease (Eke *et al.*, 2012). Caries is also highly prevalent in the majority of adults (Dye *et al.*, 2012). PD destroys bone and connective tissues of the gingiva and is associated with increased systemic inflammation and risk for inflammatory diseases (Blaizot *et al.*, 2009; Sfyroeras *et al.*, 2012). Caries arises from demineralization and destruction of the hard tissues of the tooth caused by bacterial fermentation and acid production. Regular adult dental prophylaxis directed at prevention of PD and caries is one of the most widely used health care services (Wall and Brown, 2003). The approximately 500 million annual dental visits cost more than $100 billion (Chronic Disease Prevention and Health Promotion, 2012), and routine preventive visits account for 76% of dental services (Smithwick, 2012).

Regular control of oral microbial biofilms prevents periodontitis and caries (Axelsson and Lindhe, 1981). Some risk factors, most prominently smoking, diabetes, and certain genetic variations, are associated with more severe and progressive PD (Van Dyke and Sheilesh, 2005), and previous caries experience and levels of cariogenic bacteria are among the risk factors associated with future caries lesions (Fontana and Zero, 2006; Ito *et al.*, 2011). In spite of this information, the present preventive model rests on the tacit assumption that all adults are at equal risk, therefore needing biannual professional preventive measures, as adopted in many health systems. Scant evidence supports this preventive care frequency in adults (Sheiham, 1977; Rosen *et al.*, 2004; Beirne *et al.*, 2007; Clarkson *et al.*, 2009; Ito *et al.*, 2012).

We used pre-defined criteria to stratify adults without a periodontitis diag-

Published in Journal of Dental Research, 2013

Giannobile was editor in chief

- Giannobile et al, 2013
- Attempted to utilize a precision public health approach to stratify adults into high and low risk categories for periodontitis
  - Retrospective study of insurance claims database of over 5,000 adults
  - Based on **diabetes, smoking and interleukin-1 genotype**
- Used risk-based results to evaluate tooth loss with 1 vs. 2 annual preventive visits
- Initial results appeared to demonstrate clinical utility
  - reduce to 1 annual preventive visit for adults with no risk factors

Importance of Critical Review of Precision Public Health Research Prior to Implementation:
Interleukin-1 & Preventive Dental Care (continued)

ELSEVIER

The Journal of the American Dental Association

Volume 146, Issue 3, March 2015, Pages 164-173.e4

Original Contributions

Genetic Screening

Interleukin 1 genetic tests provide no support for reduction of preventive dental care

Scott R. Diehl PhD, Fengshen Kuo MS, PhD, Thomas C. Hart DDS, PhD

Available online 25 February 2015.

- Diehl et al, 2015
- Re-analyzed initial findings from Giannobile et al study
- No evidence for the interleukin-1 genotype and association with tooth loss
- Results could not be used to reduce preventive dental care by differentiating high and low risk patients
- **Need for additional clinical validity and utility studies**
- **Not a Tier 1 genetic test for use in populations**

ADANews

Scientists agree to disagree on genetic testing

October 14, 2014

By James Berry

An atmosphere of professionalism and cordiality prevailed Oct. 11 in Room 214B at San Antonio's Henry B. Gonzalez Convention Center — but there was a hint of restrained disagreement in the air as well.

Scientists from academia, research and industry had come together to explore current science and clinical applications for genetic testing in oral medicine. It's a controversial field of scientific exploration, the controversy resting heavily on questions about the clinical application of genetic tests already on the market.

Welcoming a panel of five experts and an audience of about 200, Dr. Daniel M. Meyer, senior vice president, ADA Division of Science, noted that the morning's forum was part of a tradition begun several years earlier at the ADA's annual meeting.

Its purpose, he said, was to bring scientists and clinicians together to "talk about issues where the answers aren't necessarily clear."

Strongly countering Dr. Kornman's remarks was Scott Diehl, Ph.D., professor in oral biology and health informatics at Rutgers University, who noted that he had been studying periodontitis and working in the field of genetics for some 30 years.

"It is my pleasure to be here," he told the audience, "but not my pleasure to report to you that I am forced to disagree with [Dr. Kornman's] conclusions. I do not believe there is any scientific support for the IL-1 genetic test."

Valid genetic testing for periodontitis may emerge in the future, said Dr. Diehl, "but I don't think we have it yet."

He also questioned the value of focusing solely on the IL-1 gene. "We have the whole genome to cover, and that we've been covering," he said, adding that thousands of other genes are "biologically relevant" and have "stronger statistical association with disease."

Concluding the panel presentations, Dr. John Gunsolley, director, Clinical Research Unit, Virginia Commonwealth University School of Dentistry, talked about evaluating the clinical utility and plausibility of genetic testing. He also talked about common risk factors and the importance of plaque control.

There was general agreement among the panelists that genetic testing is a complex topic, especially as it applies to clinical dentistry and medicine. Panel members stressed the need for more education on genetics in dental schools.

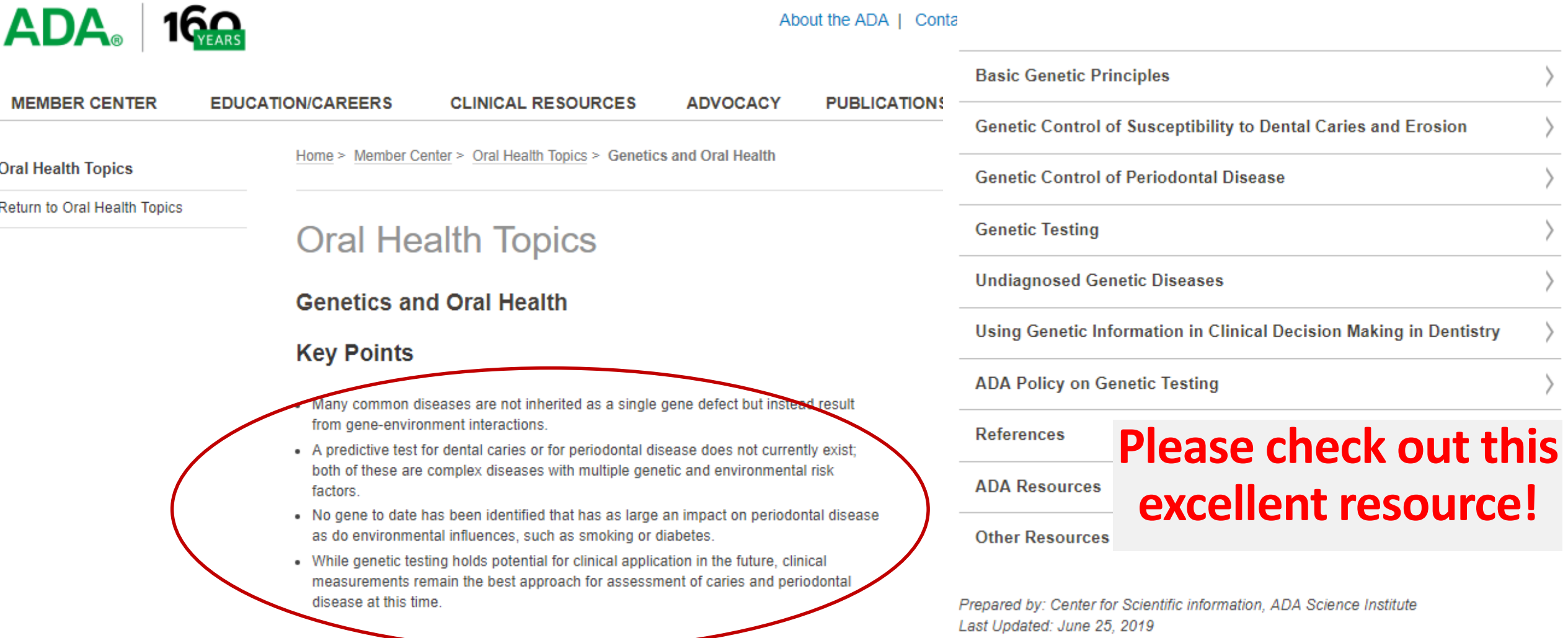
Audience members asked a range of thoughtful questions, touching on such issues as the importance of home care, the future of salivary diagnostics and testing for the human papilloma virus.

In the end, differing points of view were fairly aired and professionally received. And the journey of science that Dr. Glick described continued on for another day.

ttps://www.ada.org/en/publications/ada-news/2014-archive/october/scientists-agree-to-disagree-on-genetic-testing

ADA Genetics & Oral Health, 2017 and updated 2019

Example of Core Public Function of Assurance



ADA | 160 YEARS

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MEMBER CENTER EDUCATION/CAREERS CLINICAL RESOURCES ADVOCACY PUBLICATIONS

Oral Health Topics

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Oral Health Topics

Genetics and Oral Health

Key Points

- Many common diseases are not inherited as a single gene defect but instead result from gene-environment interactions.
- A predictive test for dental caries or for periodontal disease does not currently exist; both of these are complex diseases with multiple genetic and environmental risk factors.
- No gene to date has been identified that has as large an impact on periodontal disease as do environmental influences, such as smoking or diabetes.
- While genetic testing holds potential for clinical application in the future, clinical measurements remain the best approach for assessment of caries and periodontal disease at this time.

Basic Genetic Principles

Genetic Control of Susceptibility to Dental Caries and Erosion

Genetic Control of Periodontal Disease

Genetic Testing

Undiagnosed Genetic Diseases

Using Genetic Information in Clinical Decision Making in Dentistry

ADA Policy on Genetic Testing

References

ADA Resources

Other Resources

Prepared by: Center for Scientific information, ADA Science Institute
Last Updated: June 25, 2019

Please check out this excellent resource!

https://www.ada.org/en/member-center/oral-health-topics/genetics-and-oral-health

Interleukin-1 & Preventive Dental Care (continued): Highlights Ethical, Legal and Social Issues (ELSI)

genomeweb

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Home » Business, Policy & Funding » Business News » Controversial Gum Disease Risk Test Highlights Precision Medicine Marketing, Regula

Controversial Gum Disease Risk Test Highlights Precision Medicine Marketing, Regulatory Issues

Jul 11, 2017 | Turna Ray

NEW YORK (GenomeWeb) – Interleukin Genetics' decision to stop selling a genetic test it claims can assess the risk of gum disease is welcome news for some experts in the field of dentistry who have long had serious concerns about the science underlying the product.

They contend that the test should have never come to market in the first place, but remained available to patients far too long because the leadership at Interleukin had influence within the dental research community, a group that is not well-enough versed in genetics to be able to parse the available data themselves.

In April, the American Dental Association published an educational brief for dentists on the genetics of oral health and noted that periodontal disease is a complex disease that may be due to a number of genetic and environmental factors. The ADA said it knows genetic tests are being marketed for gauging risk for gum disease.

https://www.genomeweb.com/molecular-diagnostics/controversial-gum-disease-risk-test-highlights-precision-medicine-marketing#.XTjIvbxKjIU

- Commercial genetic testing lab began offering testing based on the Giannobile et al risk-based study
  - Founder of company was one of co-authors
  - Estimated that insurers could save $4.8 billion
  - Both a health plan and large corporation in Michigan had invested in genetic testing company and funded Giannobile study
- Employee wellness plan from both companies decided to include in risk-based benefit plan starting in 2013
  - Employees would receive only one covered cleaning per year unless deemed at high-risk based on genetic test or other risk factors
  - Employees could decline genetic test but then would be limited to one covered cleaning

ADA Policy on Genetic Testing for Payers & Laboratories, 2017

Core Public Health Function of Policy Development

ADA Adopts Policy on Genetic Testing

October 27, 2017

Contact Information:
mediarelations@ada.org

CHICAGO, October 27, 2017 — The American Dental Association at its annual meeting in Atlanta adopted a policy on genetic testing calling for insurers to:

- demonstrate that genetic tests used to determine eligibility for benefit coverage of specific oral health services are scientifically valid
- disclose financial relationships between manufacturer and payer
- be transparent about conflicts of interest between the test manufacturer, payer and study investigators
- provide independent third party agency confirmation of test validity and reliability for the intended purpose
- and an analysis of how utilization of the test will affect health outcomes and plan costs

The policy states, "Health professions will experience a growth of such products and tests in the coming years and [dentists] will need a mechanism to assess the claims and counter claims so that we may best serve our patients and advocate for the needs of the public."

ADA Policy on Genetic Testing

Genetic Testing for Risk Assessment (Trans.2017:266)

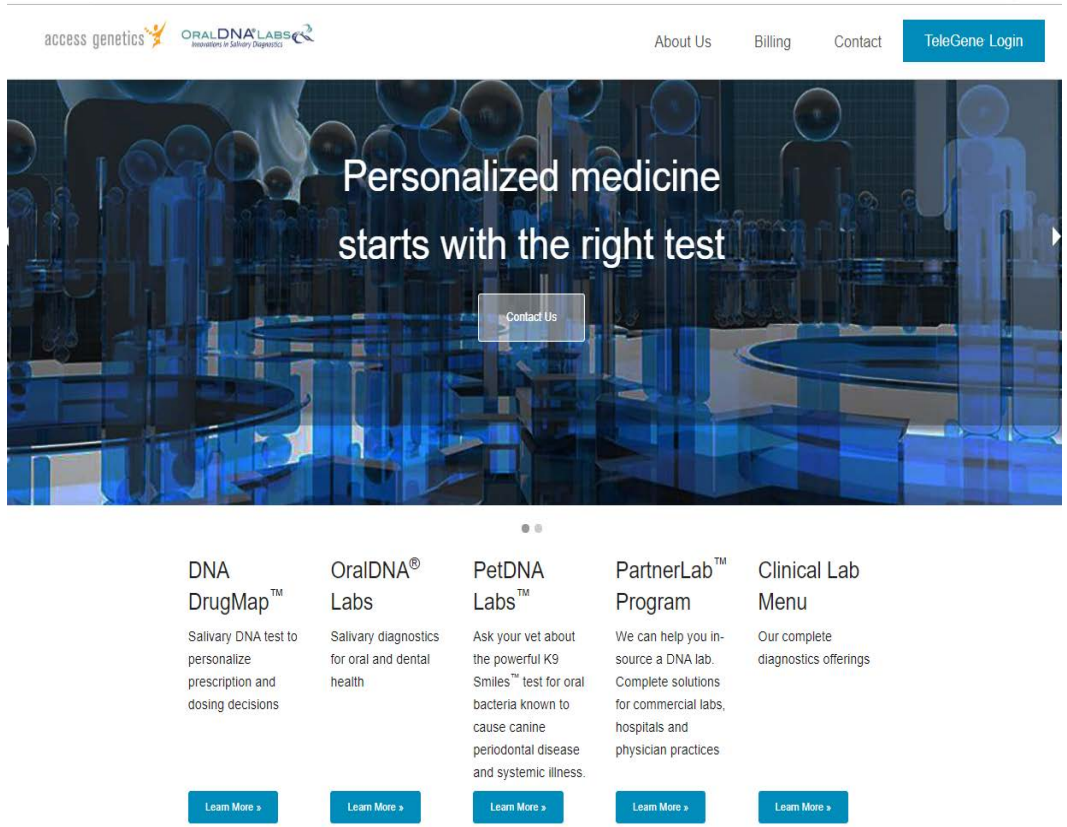
Resolved, that for the health and well-being of the public, the American Dental Association believes that any payer organization using a genetic test to determine eligibility for benefit coverage for specific oral healthcare services and any manufacturer of a test(s) used in such an effort must publish specific information on:

- Confirmation from an independent third party agency of test validity and reliability for the intended purpose
- Analysis on how this specific plan design will impact health outcomes and plan costs
- Disclosure of financial relationships between the manufacturer and payer
- Disclosure of bias and conflict of interest between the test manufacturer, investigators providing evidence and literature used to promote the test and plan design and with the payer organization

American Dental Association
Adopted 2017

https://www.ada.org/en/press-room/news-releases/2017-archives/october/ada-adopts-policy-on-genetic-testing

July 2019: What would you do with this information?



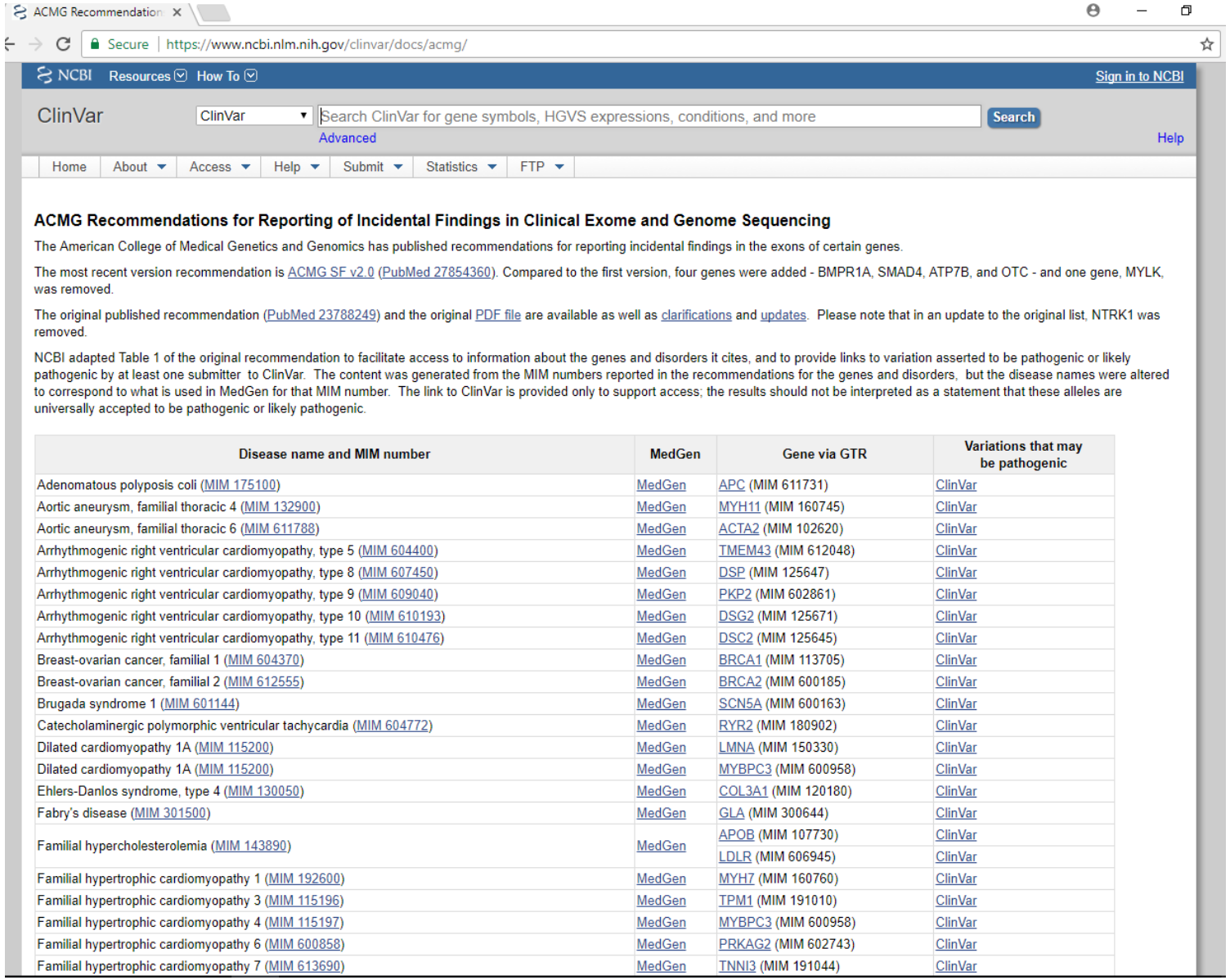
https://www.oraldna.com/

Newer Genomic Technologies: Next Generation Sequencing (NGS)

- NGS allows sequencing hundreds to thousands of genes at one time
- Offered by several genetic testing laboratories for clinical and/or research purposes
- Whole Exome Sequencing (WES)
  - Targeted view of the protein-coding regions of the genome
  - Includes ~85% of disease-related variants
- Whole Genome Sequencing (WGS)
  - Analyzes entire genome
- When used for clinical purposes, testing is typically ordered for diagnostic reasons due to suspected genetic etiology based on clinical findings
- Secondary finding
  - Pathogenic findings unrelated to the primary clinical reason for testing

American College of Medical Genetics and Genomics (ACMG) Secondary Findings Recommendations

- Recommends labs report secondary findings when perform clinical exome and genome sequencing tests on list of genes known to cause **severe disease and clinically relevant actions available**
- List currently includes 59 genes (updated in 2016)
- ACMG working group curate and updates list periodically



ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

The American College of Medical Genetics and Genomics has published recommendations for reporting incidental findings in the exons of certain genes.

The most recent version recommendation is ACMG SF v2.0 (PubMed 27854360). Compared to the first version, four genes were added - BMPR1A, SMAD4, ATP7B, and OTC - and one gene, MYLK, was removed.

The original published recommendation (PubMed 23788249) and the original PDF file are available as well as clarifications and updates. Please note that in an update to the original list, NTRK1 was removed.

NCBI adapted Table 1 of the original recommendation to facilitate access to information about the genes and disorders it cites, and to provide links to variation asserted to be pathogenic or likely pathogenic by at least one submitter to ClinVar. The content was generated from the MIM numbers reported in the recommendations for the genes and disorders, but the disease names were altered to correspond to what is used in MedGen for that MIM number. The link to ClinVar is provided only to support access; the results should not be interpreted as a statement that these alleles are universally accepted to be pathogenic or likely pathogenic.

Disease name and MIM number	MedGen	Gene via GTR	Variations that may be pathogenic
Adenomatous polyposis coli (MIM 175100)	MedGen	APC (MIM 611731)	ClinVar
Aortic aneurysm, familial thoracic 4 (MIM 132900)	MedGen	MYH11 (MIM 160745)	ClinVar
Aortic aneurysm, familial thoracic 6 (MIM 611788)	MedGen	ACTA2 (MIM 102620)	ClinVar
Arrhythmogenic right ventricular cardiomyopathy, type 5 (MIM 604400)	MedGen	TMEM43 (MIM 612048)	ClinVar
Arrhythmogenic right ventricular cardiomyopathy, type 8 (MIM 607450)	MedGen	DSP (MIM 125647)	ClinVar
Arrhythmogenic right ventricular cardiomyopathy, type 9 (MIM 609040)	MedGen	PKP2 (MIM 602861)	ClinVar
Arrhythmogenic right ventricular cardiomyopathy, type 10 (MIM 610193)	MedGen	DSG2 (MIM 125671)	ClinVar
Arrhythmogenic right ventricular cardiomyopathy, type 11 (MIM 610476)	MedGen	DSC2 (MIM 125645)	ClinVar
Breast-ovarian cancer, familial 1 (MIM 604370)	MedGen	BRCA1 (MIM 113705)	ClinVar
Breast-ovarian cancer, familial 2 (MIM 612555)	MedGen	BRCA2 (MIM 600185)	ClinVar
Brugada syndrome 1 (MIM 601144)	MedGen	SCN5A (MIM 600163)	ClinVar
Catecholaminergic polymorphic ventricular tachycardia (MIM 604772)	MedGen	RYR2 (MIM 180902)	ClinVar
Dilated cardiomyopathy 1A (MIM 115200)	MedGen	LMNA (MIM 150330)	ClinVar
Dilated cardiomyopathy 1A (MIM 115200)	MedGen	MYBPC3 (MIM 600958)	ClinVar
Ehlers-Danlos syndrome, type 4 (MIM 130050)	MedGen	COL3A1 (MIM 120180)	ClinVar
Fabry's disease (MIM 301500)	MedGen	GLA (MIM 300644)	ClinVar
Familial hypercholesterolemia (MIM 143890)	MedGen	APOB (MIM 107730)	ClinVar
		LDLR (MIM 606945)	ClinVar
Familial hypertrophic cardiomyopathy 1 (MIM 192600)	MedGen	MYH7 (MIM 160760)	ClinVar
Familial hypertrophic cardiomyopathy 3 (MIM 115196)	MedGen	TPM1 (MIM 191010)	ClinVar
Familial hypertrophic cardiomyopathy 4 (MIM 115197)	MedGen	MYBPC3 (MIM 600958)	ClinVar
Familial hypertrophic cardiomyopathy 6 (MIM 600858)	MedGen	PRKAG2 (MIM 602743)	ClinVar
Familial hypertrophic cardiomyopathy 7 (MIM 613690)	MedGen	TNNI3 (MIM 191044)	ClinVar

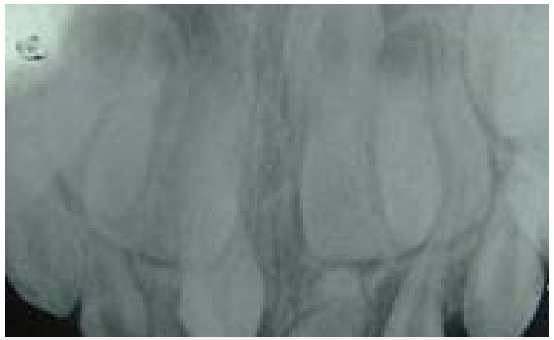
https://www.ncbi.nlm.nih.gov/clinvar/docs/acmg/

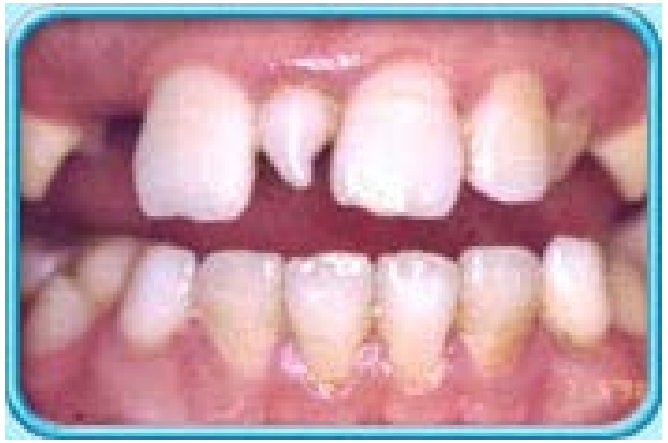
Examples of Secondary Finding Genes to Report with Potential Importance to Dental Public Health Professionals

Condition	Gene	Relevance to Oral Health
Adenomatous polyposis coli (FAP)	APC	Teeth and tongue findings could be key to referral for genetic screening/diagnosis
Peutz-Jegher syndrome	STK11	Mouth features could be key to referral for genetic screening/diagnosis
PTEN hamartoma tumor syndrome (Cowden syndrome)	PTEN	Teeth and tongue findings could be key to referral for genetic screening/diagnosis
Long QT syndrome	KCNQ1, KCNH2, SCN5A	Medications and surgical environment for dental procedures
Malignant hyperthermia	CACNA1S	Medications and surgical environment (general anesthetics and stress) for dental procedures consider
Loeys-Dietz syndrome	TGFBR1, TGFBR2	Craniofacial features and bifid uvula/cleft palate consider for genetics referral
Brugada syndrome 1	SCN5A	Surgery complicated and consider avoiding local anesthesia during dental procedures

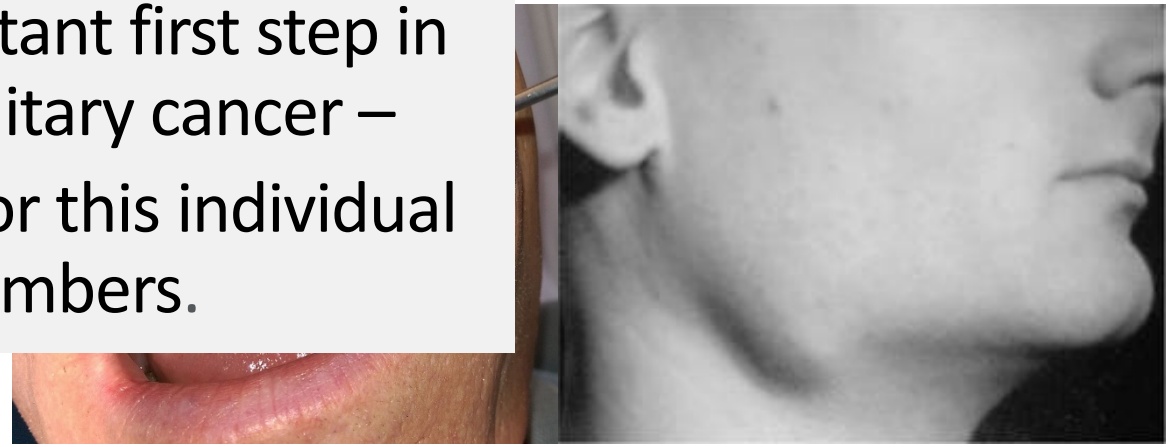
Familial Adenomatous Polyposis Coli (FAP)

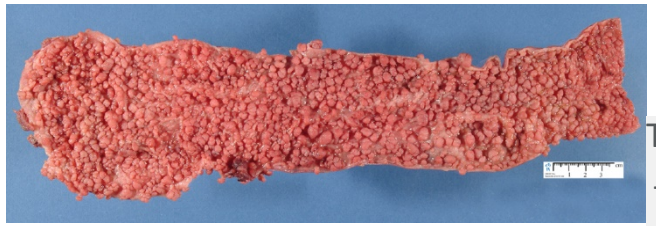
- Accounts for 1% of all colorectal cancers
- Most common hereditary polyposis
- Autosomal dominant
  - 100% penetrance; untreated polyposis leads to ~100% risk of cancer
  - Caused by mut
- Classic FAP: more
  (attenuated FAP le
- Risk of other extra
  osteomas (50-90%
- Retinal pigmentat
- **Dental anomalies**
  - **Supernumerary teeth (11-27% of patients with FAP)**
  - **Unerupted teeth**
  - **Congenital absence of one or more teeth**
- Management: earlier and more frequent cancer screening; prophylactic colectomy typically prior to age 25





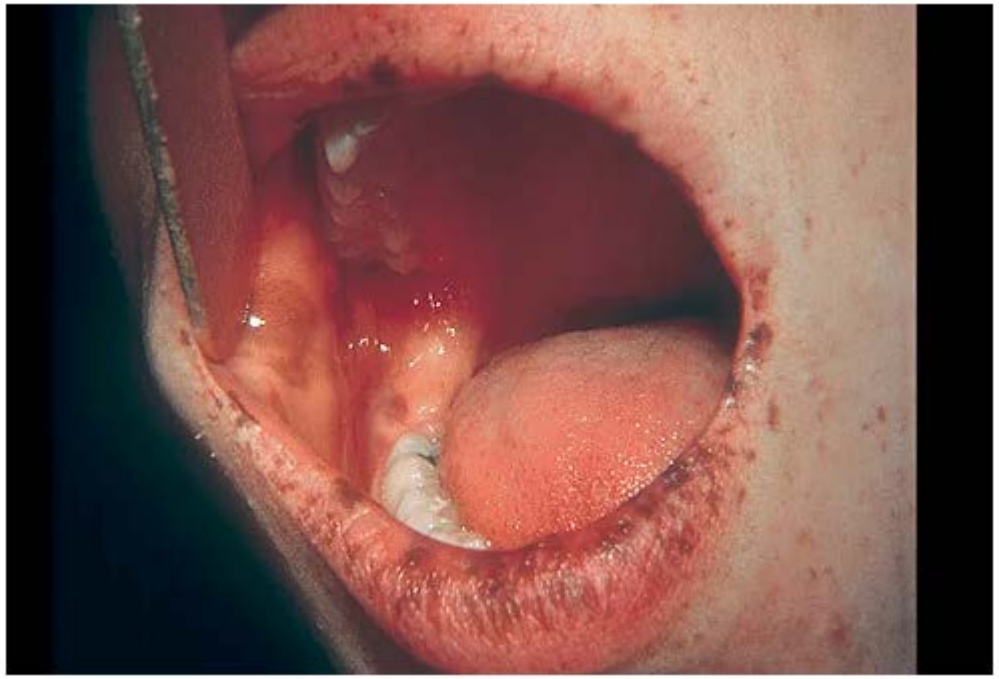
The identification of such dental anomalies in the presence of personal and/or family history of cancer could be an important first step in identification of this hereditary cancer – before the onset of cancer for this individual and their family members.





Thank you to Jess Stoll, MS, CGC from University of Chicago for sharing slides

Peutz Jegher Syndrome (PJS)



https://www.medicinenet.com/image-collection/peutz-jeghers_syndrome_picture/picture.htm

- Rare autosomal dominant hereditary cancer
- Caused by mutation in STK11 gene
- Diagnostic criteria: confirmed hamartomatous GI polyp with distinctive morphology plus two of the following:
  - Small bowel polyposis
  - **Mucocutaneous hyperpigmentation of the buccal mucosa, lips**, fingers, toes and/or external genitalia
    - Dark blue to dark brown
    - Present in over 95% of people with PJS
    - Generally appear in childhood; after age 25, may fade and less noticeable
  - Family history of PJS
- ~63% risk of cancer by age 60; increased risk of GI tract cancers (colorectal, pancreatic, esophageal, stomach, small bowel), thyroid, breast, and gynecological cancers
- Management: Earlier and more frequent cancer screening (e.g. baseline colonoscopy and upper GI endoscopy begin at age 8; breast MRI begin at age 25; etc)

Cowden Syndrome (PTEN)

- Autosomal dominant hereditary cancer
- Usually due to mutation in PTEN gene
- Major clinical features: breast cancer; **thyroid** cancer; endometrial cancer; **macrocephaly**
- Other cancers include colorectal and renal cancer
- Other clinical features include:
  - **Facial papules and trichilemmomas around mouth, eyes and nostrils**
  - **Papillomatous papules (numerous 1-3 mm smooth white spots on gums and palate)**
  - GI hamartomas, lipomas, papillomas
- Management: earlier and more frequent cancer screening; discuss prophylactic mastectomy or hysterectomy

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5134167/

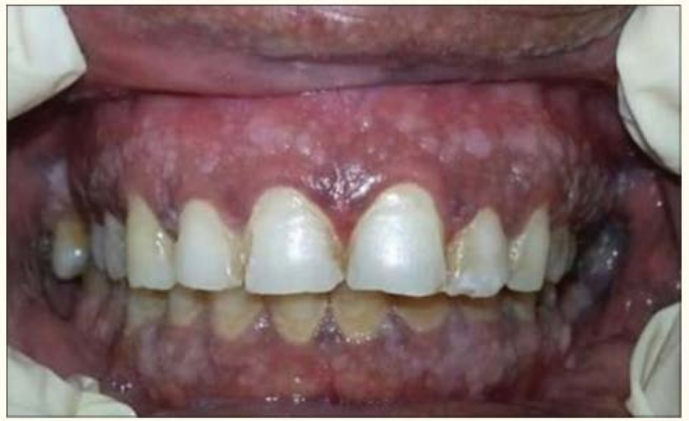


Figure 2

Multiple papules on gingiva giving rise to a cobbl

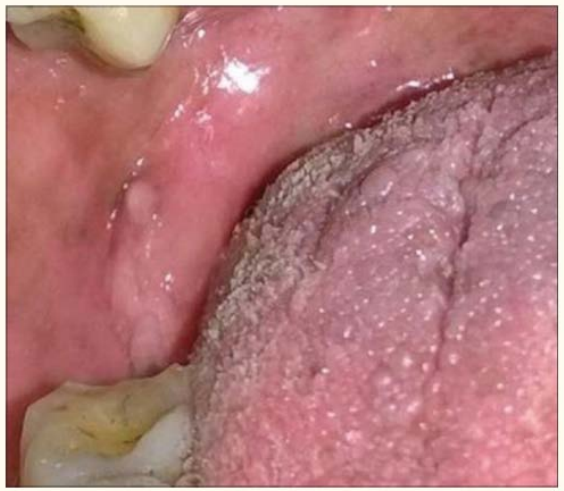
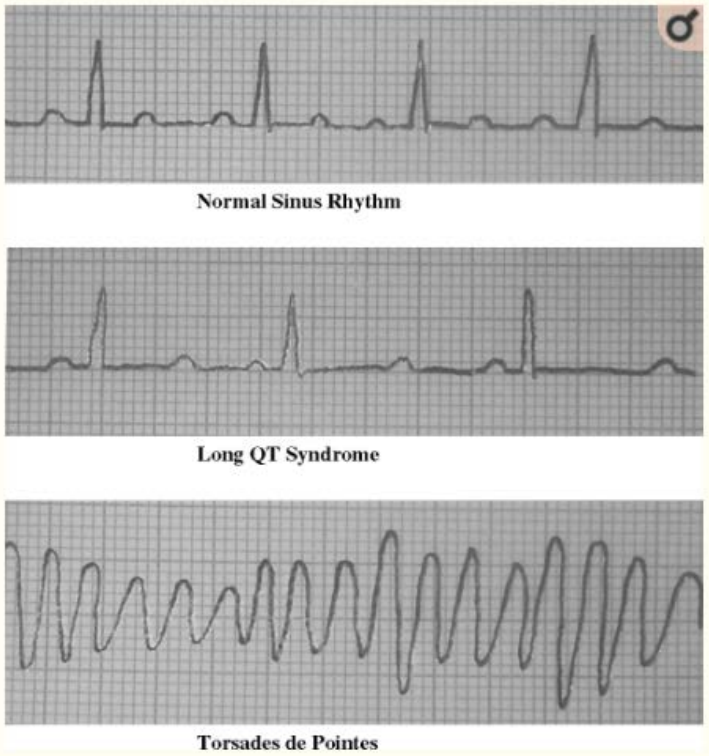


Figure 3

Multiple papules on tongue giving rise to a moriform appearance and soft nodule noted on right retromolar region

Long QT Syndrome (LQTS)

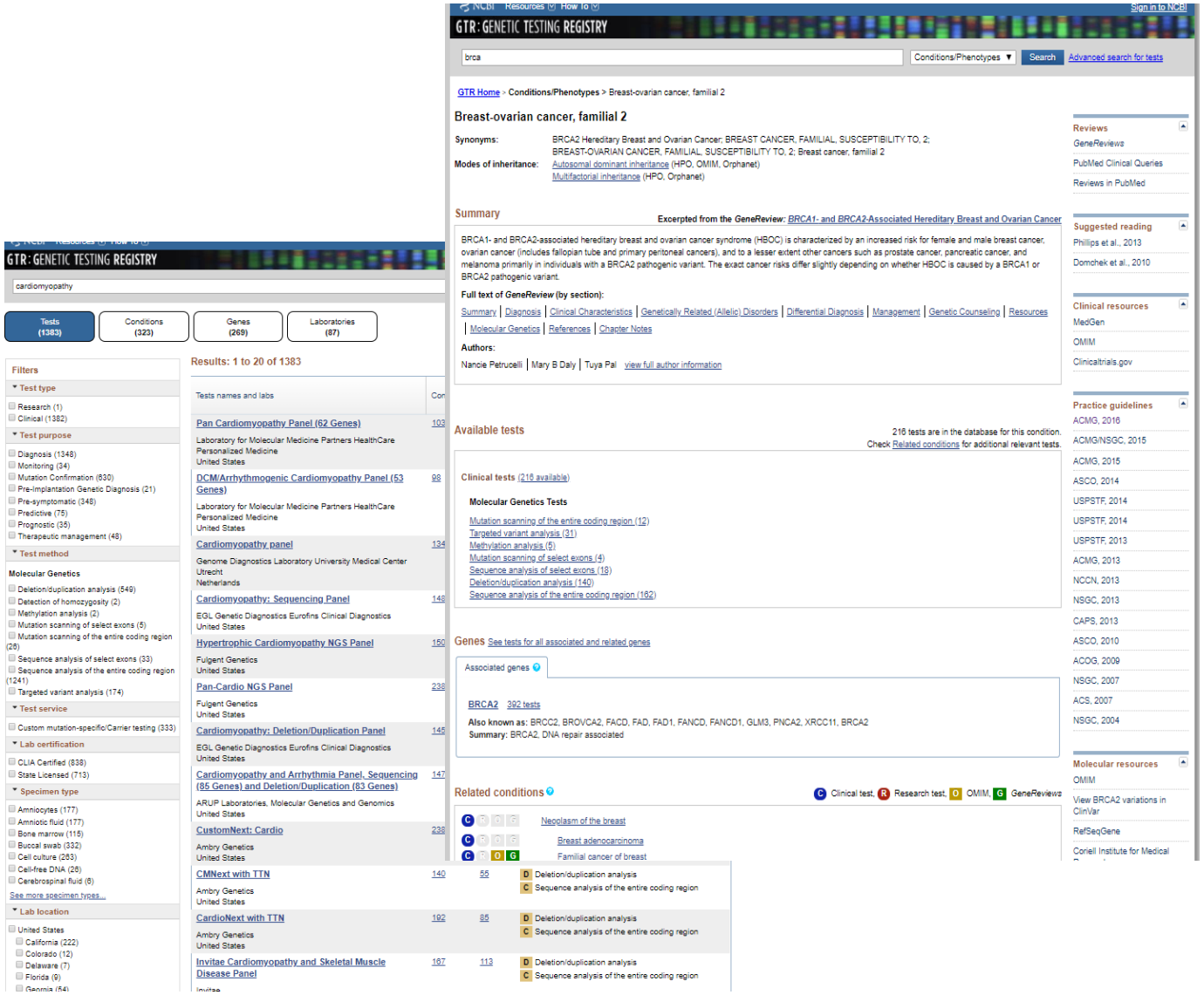
- Autosomal dominant
- Due to mutations in KCNQ1, KCNH2 or SCN5A genes
- QT prolongation, T-wave abnormalities, ventricular tachycardia/ torsades de pointes
- Cardiac events most common from pre-teens through 20's, but variability
  - Syncope and cardiac events often during exertion or excitement
  - ECG changes are most commonly elicited by physical activity, emotional stress, and certain medications
- Can result in sudden cardiac or unexplained death
  - Typically normal autopsy; postmortem genetic testing, personal and family history is vital in diagnosis
- Treatment: avoidance of specific drugs and intense physical activity and emotional stress; beta-blockers, ICD, surgery
- **Dental Preventive Measures:** evaluation by cardiac specialist, use of anxiolytic protocols, avoidance of drugs that prolong the QT interval, consider anesthesiologists for procedures in which anxiety and adrenergic stimulation would not be suppressed sufficiently in an ambulatory setting



Karp & Moss, J Am Dental Assoc, 2006

Rochford & Seldin, Anest Prog, 2009

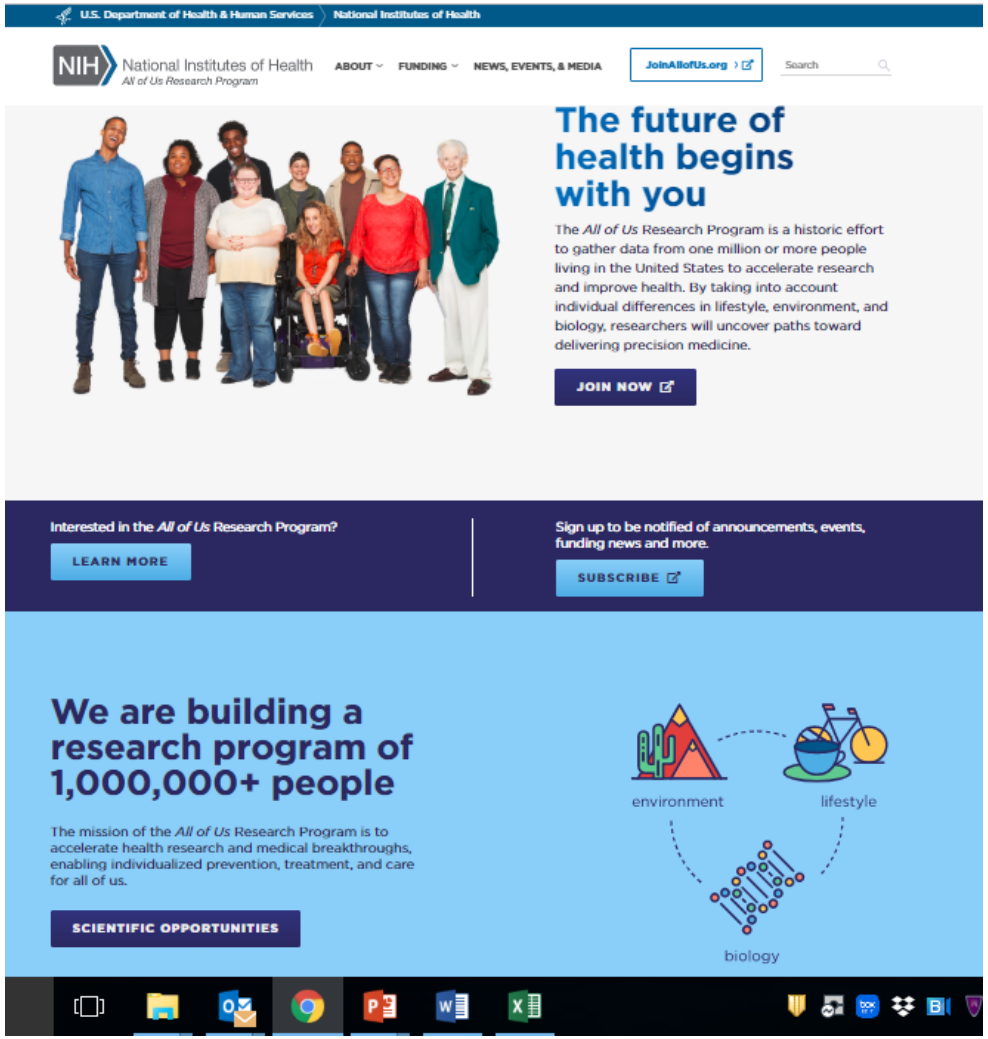
GTR: Genetic Testing Registry



- Provides central location to locate current information about laboratories and genetic tests
  - Purpose
  - Methodology
  - Validity
  - Utility
  - Credentials

http://www.ncbi.nlm.nih.gov/gtr/

The All of Us Research Program (The Precision Medicine Initiative)



https://allofus.nih.gov/

Review of Today's Learning Objectives

- Name three genetic conditions that are relevant to oral health and public health genomics
  - *FAP; Cowden; Peutz Jeghers; Long QT syndrome; and several others!*
- Describe a public health approach to determine if a genetic test is ready for implementation at the clinical and/or population level
  - *Analytic Validity, Clinical Validity, Clinical Utility, ELSI (ACCE); USPSTF; EGAPP; Genomics Translation Highway*
- List two available public health genomics resources that are useful to dental public health professionals
  - *CDC OPHG website; My Family Health Portrait; Genetic Testing Registry; NSGC and ACMG genetics directories; ADA genetic testing & risk assessment policy statement; ADA Genetics & Oral Health educational resources; All of Us research*

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Feinberg School of Medicine

Thank you!