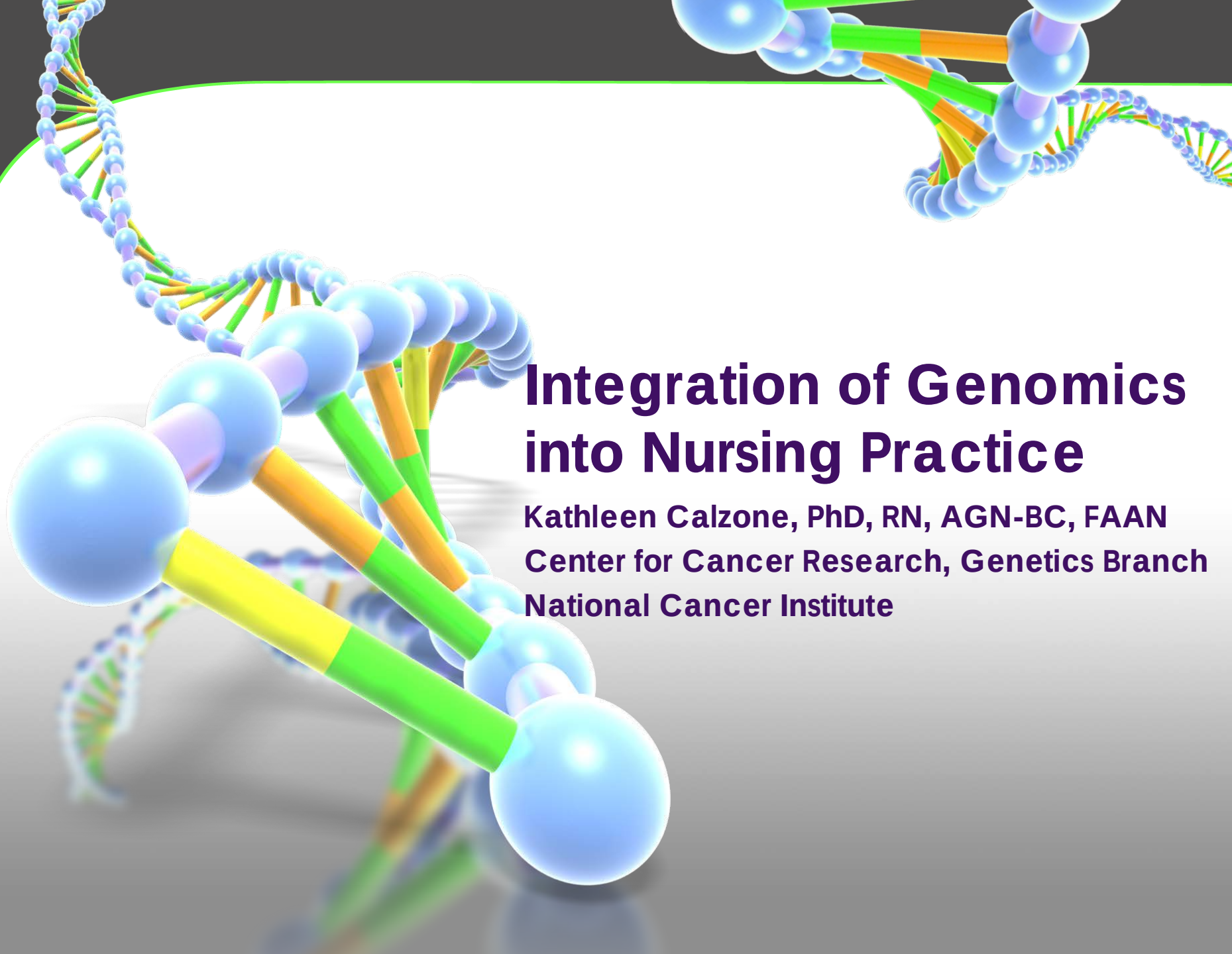


# Integration of Genomics into Nursing Practice

**Kathleen Calzone, PhD, RN, AGN-BC, FAAN**
**Center for Cancer Research, Genetics Branch**
**National Cancer Institute**

# Five Misconceptions About the Role of Genomics in Public Health

1. Genomics is about rare diseases that have a small impact on public health
   - Newborn screening
2. Genetic factors are less important than environmental, behavioral, and social determinants of health
   - Could be as many as a third of deaths annually from the 5 leading causes of deaths are potentially preventable by reducing the prevalence of known risk factors

Khoury, M. (2016). Center for Disease Control. Genomics and Health Impact Blog. Five Misconceptions About the Role of Genomics in Public Health https://blogs.cdc.gov/genomics/2016/07/13/five-misconceptions/

# Five Misconceptions About the Role of Genomics in Public Health, cont

3. Genetic factors are non-modifiable and therefore merit little or no attention when it comes to public health programs and communication strategies
   - Family history and targeted interventions
4. Genomics is about the future. Evidence for using genomic information is not sufficient for use in practice today
   - Predisposition testing, pharmacogenomics, genomic tumor profiling

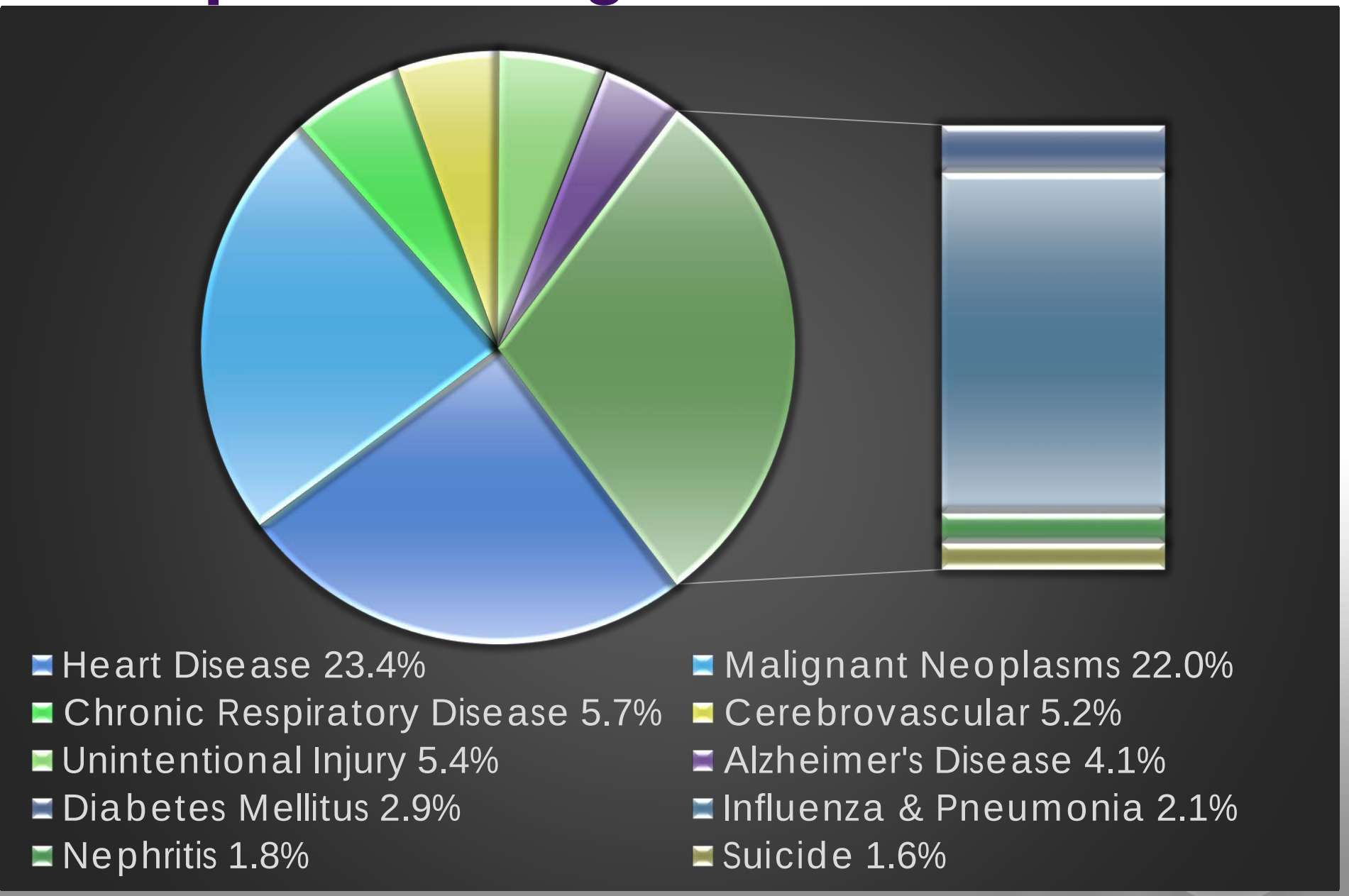
Khoury, M. (2016). Center for Disease Control. Genomics and Health Impact Blog. Five Misconceptions About the Role of Genomics in Public Health https://blogs.cdc.gov/genomics/2016/07/13/five-misconceptions/

# Five Misconceptions About the Role of Genomics in Public Health, cont

5. Genomics is in the domain of health care, and thus there is no need for public health programs to be involved
   - Pathogen genome sequencing to track infectious disease outbreak sources, spread, and susceptibility to antibiotics
     - Ebola and the spread into West Africa

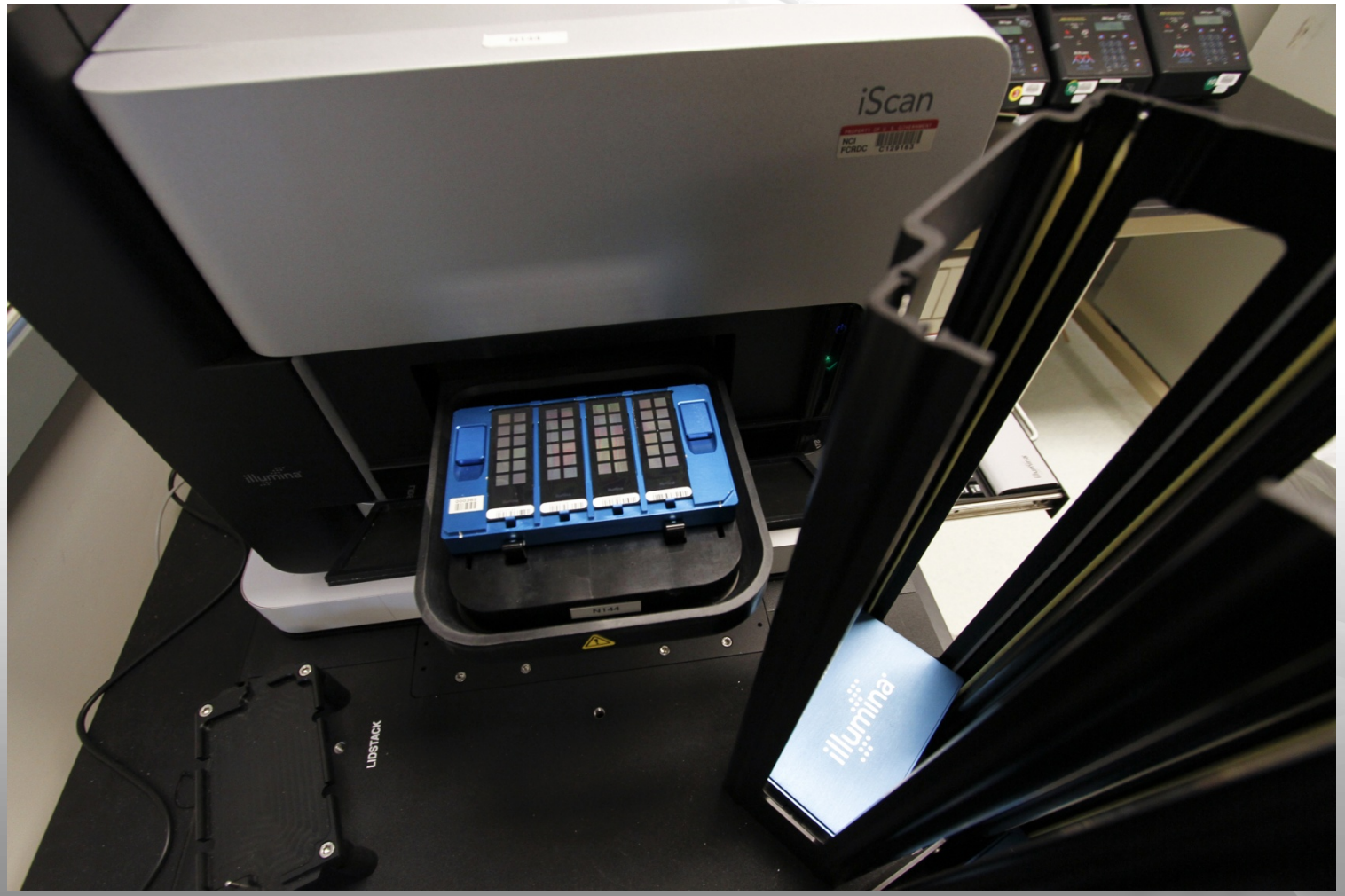
Gire et al. (2014). Genomic surveillance elucidates Ebola virus origin and transmission during the 2014 outbreak. Science, 345, 1369-1372
Khoury, M. (2016). Center for Disease Control. Genomics and Health Impact Blog. Five Misconceptions About the Role of Genomics in Public Health https://blogs.cdc.gov/genomics/2016/07/13/five-misconceptions/

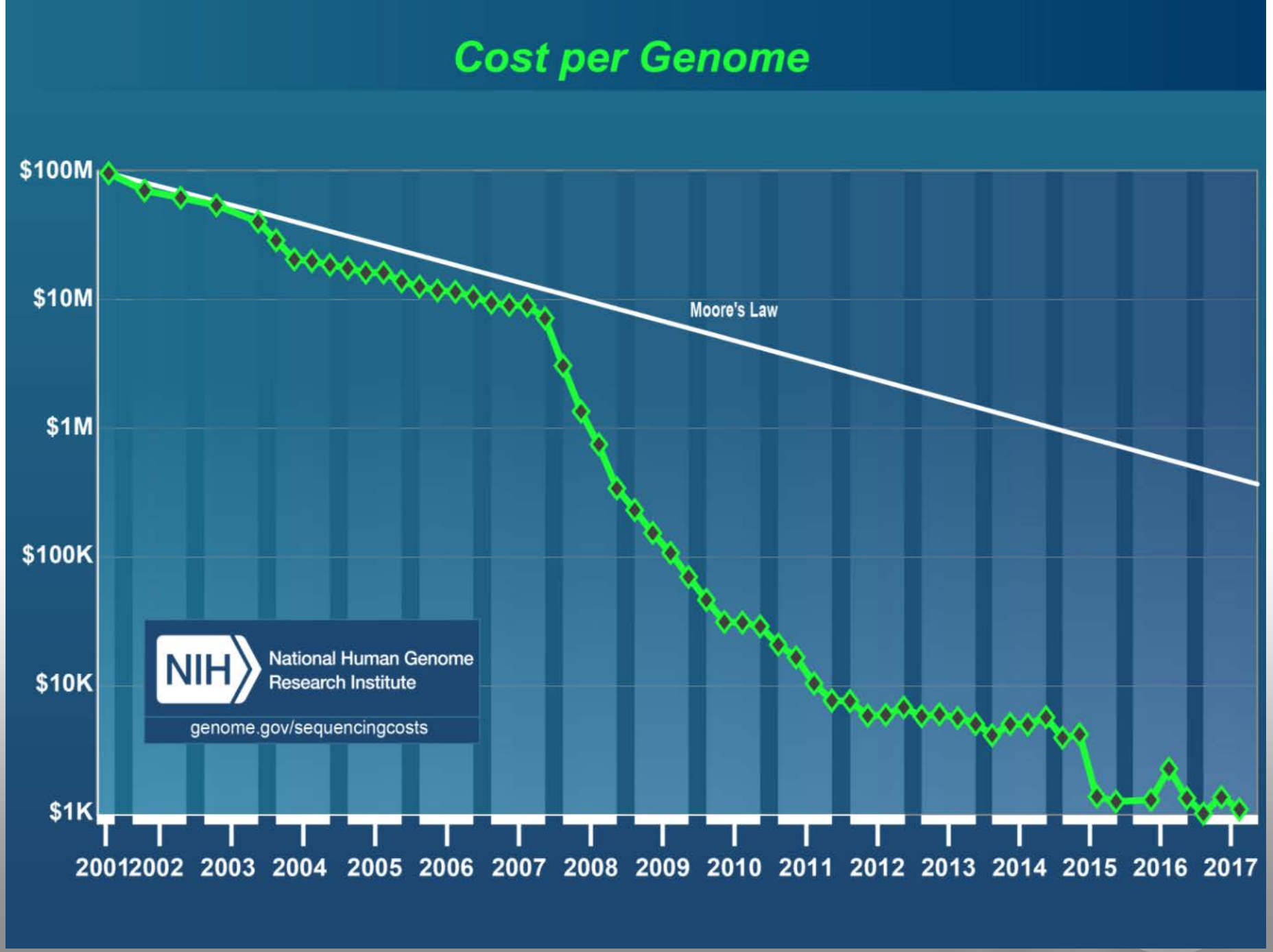
# Top 10 Leading Causes of Death




Heron et al. (2017). Deaths: Leading Causes for 2015. National Vital Statistics Reports. 66, 1-76.

# Emerging Science/Technology






https://www.genome.gov/images/content/costpergenome_2017.jpg

# The Race for the $1000 Genome Are we There Yet?

- The ability to sequence someone's entire genome for $1,000 or less
- Cost in the range of many diagnostic tests so considered realistic for routine clinical application
- Technology has outpaced our capacity for understanding this genomic information to inform and improve healthcare

Mardis, E. (2010). The $1000 genome, the $100,000 Analysis. Genome Medicine, 2: 84.
Hayden (2014). $1000 Genome. Nature, 507, 294-295,

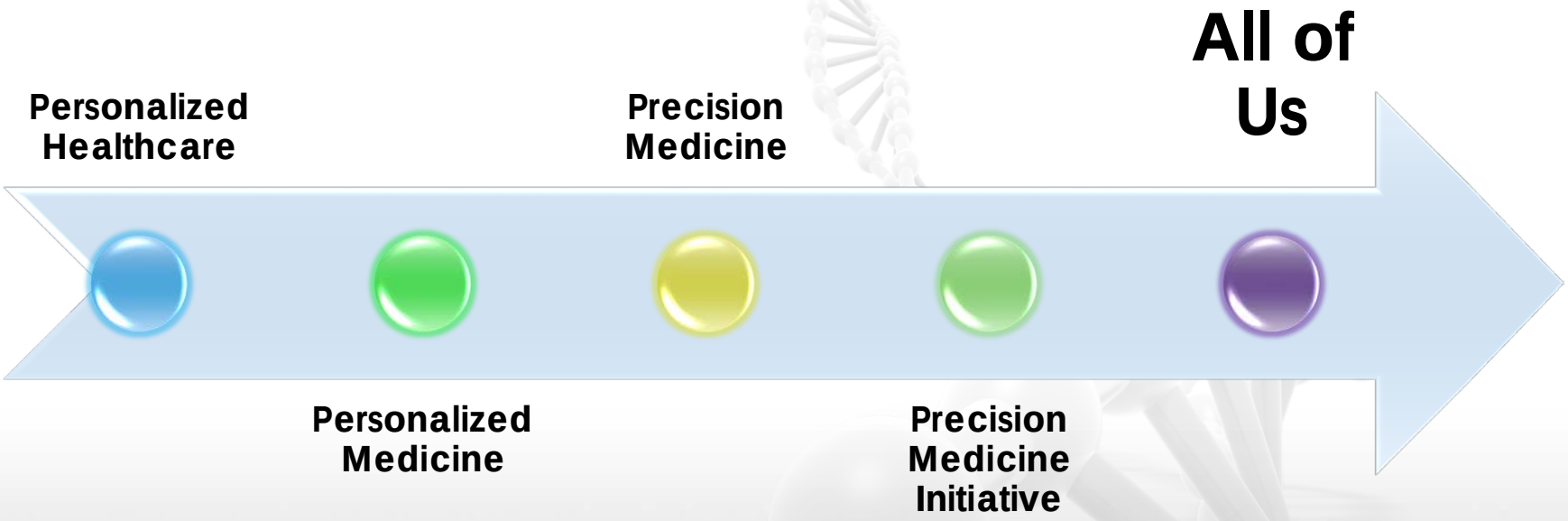
# Definitions

- **Genetics** – study of individual genes and their impact on relatively rare single gene disorders

- **Genomics** –an organism's complete set of DNA, including all of its genes

https://ghr.nlm.nih.gov/primer/hgp/genome

# Evolving Taxonomy of Genomics and Public Health



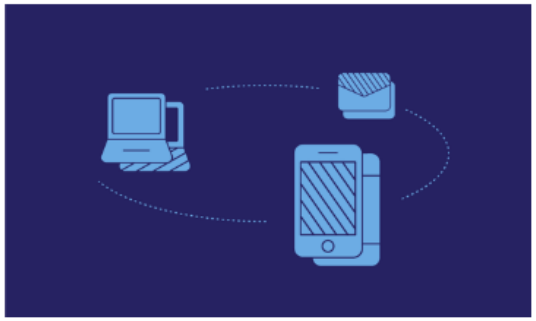

Approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.

# All of Us Research Cohort

NIH National Institutes of Health
*All of Us Research Program*

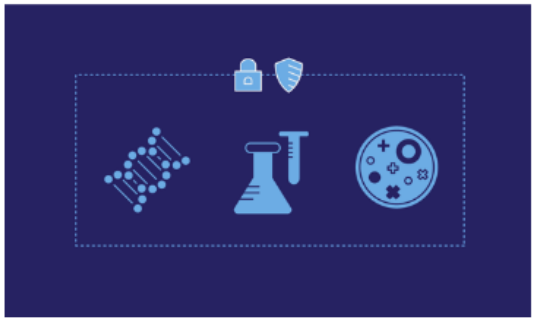
ABOUT FUNDING NEWS, EVENTS, & MEDIA SUBSCRIBE Search

**Data & Research Center**



**Participant Center**

**Health Care Provider Organizations**



**Biobank**


**Participant Technology Systems Center**

https://allofus.nih.gov/about/program-components

# Direct to Consumer Marketing and Testing

- Tests available direct to the consumer without an ordering healthcare provider
  - Varied test types and techniques
    - High penetrance diseases
    - Polygenic diseases
    - Risk Assessment
    - Low penetrance genes
    - Enhancement tests
      - Pharmacogenomic
      - Nutrigenomic
- Most require only a saliva sample
- Costs vary based on test but can be as low as $99

https://www.cancer.gov/about-cancer/causes-prevention/genetics/risk-assessment-pdq#link/_362_toc

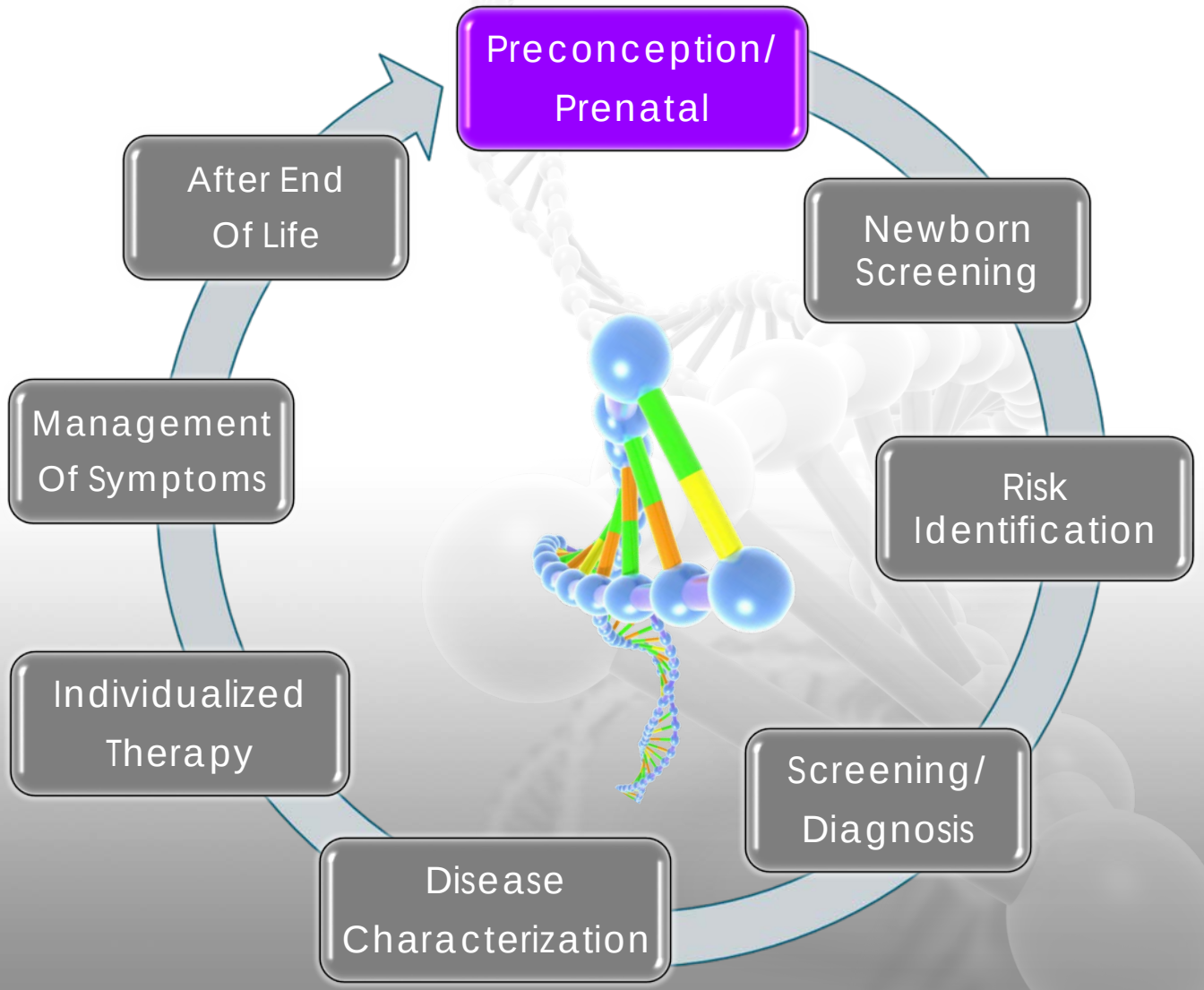
# Consumer Outcomes Associated with PGT

- PGEN Study
  - Cancer
    - Most adults with elevated cancer risk estimates did not significantly change their diet, exercise, advanced care planning, or cancer screening behaviors
  - Non-Cancer
    - PGT was associated with modest, mostly positive changes in diet and exercise but were independent of the genetic results
- Variant interpretation discordance

Tandy-Connor, S. et al. (2018). False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. GIM, Epub ahead of print.
Gray, S.W. et al. (2017). Personal Genomic Testing for Cancer Risk: Results From the Impact of Personal Genomics Study. JCO, 35, 636-644
Nielson, D.E., et al. (2017). Diet and exercise changes following direct-to-consumer personal genomic testing. BMS Med Genomics, 10, 24.

Interdisciplinary Collaboration to Improve Patient Outcomes

# Genetic and Genomic Influences Across the Healthcare Continuum




Calzone, et al. (2013). Relevance of genomics to healthcare and nursing practice. Journal of Nursing Scholarship, 45, 1-2.

# Genomics and the Nursing Workforce

| Study | N |
|---|---|
| National Nursing Workforce Study in collaboration with ANA (NNWF) | 619 |
| ANA House of Delegates (HOD) | 244 |
| National Coalition of Ethnic Minority Nurses (NCEMNA) | 389 |
| Expanding RN Scope of Practice: A Method for Introducing a New Competency into Nursing Practice (MINC) | 7798 |


Calzone, K. et al. (2018). Hospital nursing leadership-led interventions increased genomic awareness and educational intent in Magnet settings. Nursing Outlook, Epub ahead of print.

Calzone, K. et al. (2013). National Nursing Workforce Survey of Nursing Attitudes, Knowledge and Practice in Genomics. Personalized Medicine, 10, 719-728.

Badzek et al. (2013). National Nursing Leadership Survey of Attitudes, Knowledge, and Competency in Genomics. American Nurse Today, 8.

Calzone, K., et al. (2014). Expanding RN Scope of Practice: A methods for introducing a new competency into nursing practice. Journal of Nursing Regulation, 5, 40-47

# Preconception Prenatal Genetics

## Preconception

- Testing for carrier status prior to pregnancy, often for autosomal recessive disorders
  - i.e. MYH associated polyposis (MAP)
- Predisposition cancer genetic testing using chorionic villus sampling and amniocentesis using preimplantation genetic diagnosis

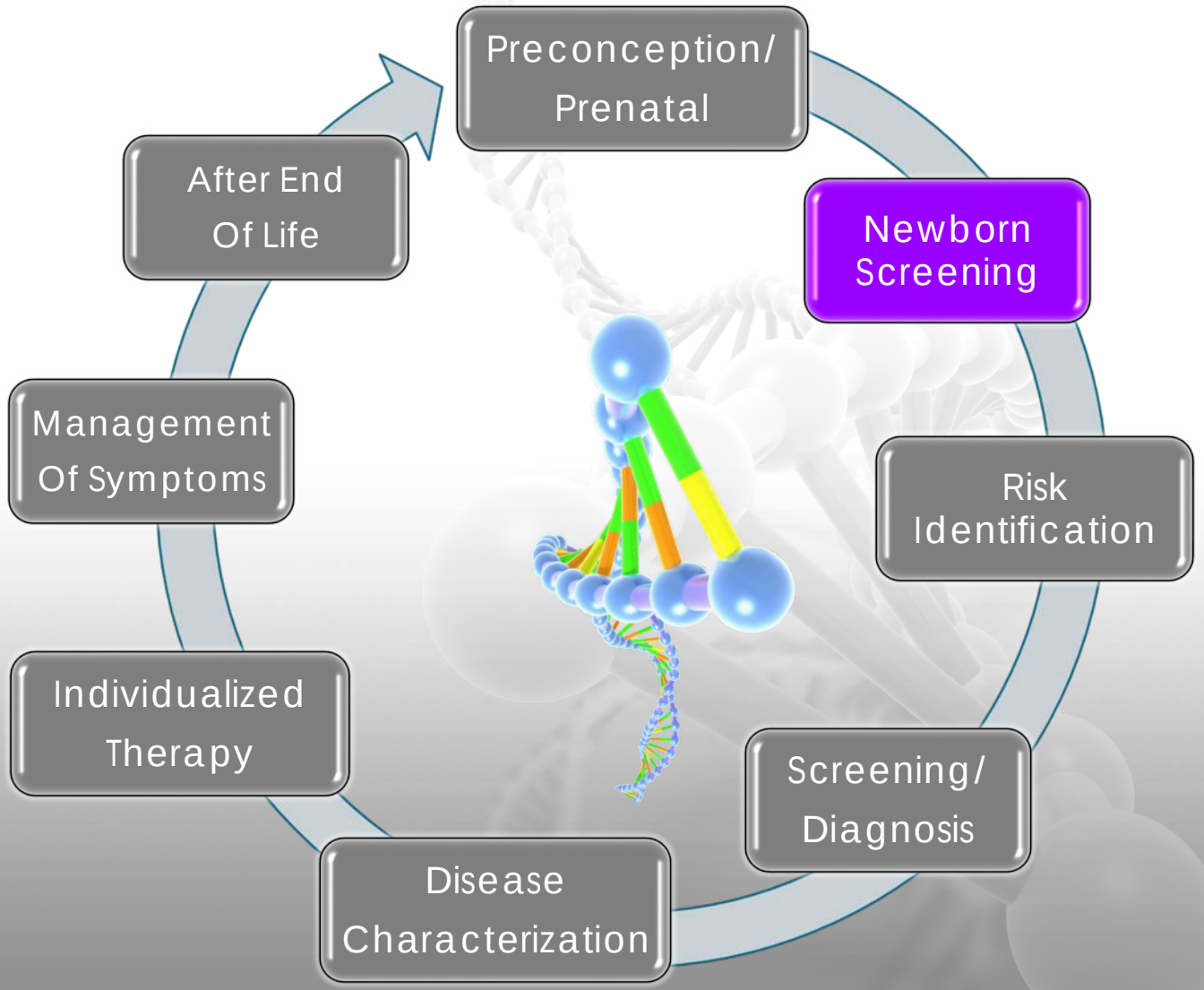
## Prenatal testing

- Performed during pregnancy
- Indications include
  - Advanced maternal age
- Non-invasive prenatal screening using cell free fetal DNA testing can identify evidence of malignancy in mother

Wou et al. (2015). Cell-free DNA versus intact fetal cells for prenatal genetic diagnostics: what does the future hold? ERMD,15(8):989-98.
Rich et al. (2014). Comparison of attitudes regarding preimplantation genetic diagnosis among patients with hereditary cancer syndromes. FC, Suppl 1:S187-92.

Interdisciplinary Collaboration to Improve Patient Outcomes

# Genetic and Genomic Influences Across the Healthcare Continuum




Calzone, et al. (2013). Relevance of genomics to healthcare and nursing practice. Journal of Nursing Scholarship, 45, 1-2.

# Newborn Screening

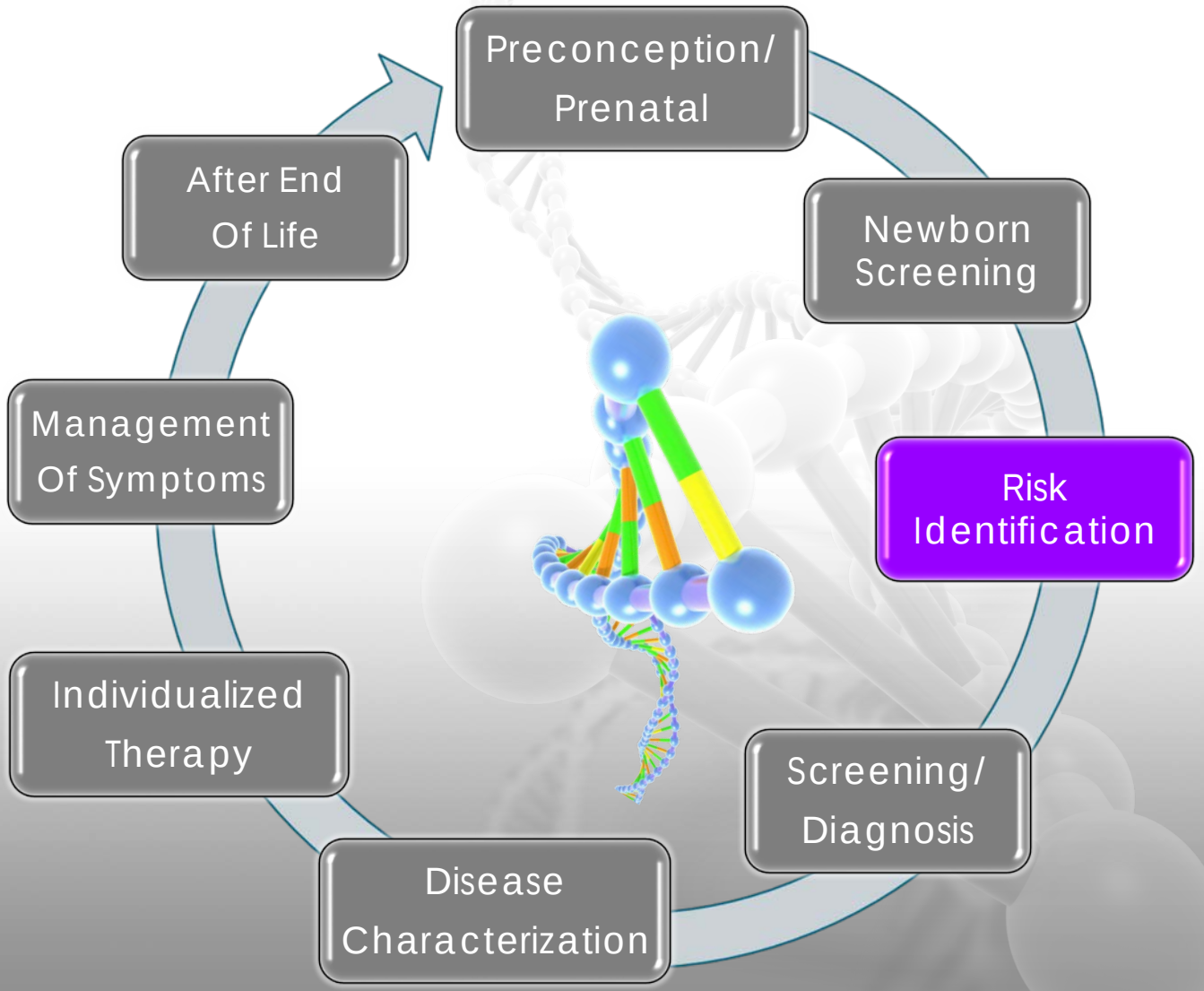
- Newborn screening consists of a public health approach to the identification and management of health conditions identifiable in the newborn
  - Approximately 4 million newborns screened annually
  - About12,500 new diagnoses as a result of testing
  - Newborn screening constitutes the most extensive use of genetics for public health benefit
  - All states provide newborn screening
- Conducted using a dried blood spot from a heel prick
- Provide false positive, false negative, or ambiguous results

# Newborn Screening, cont

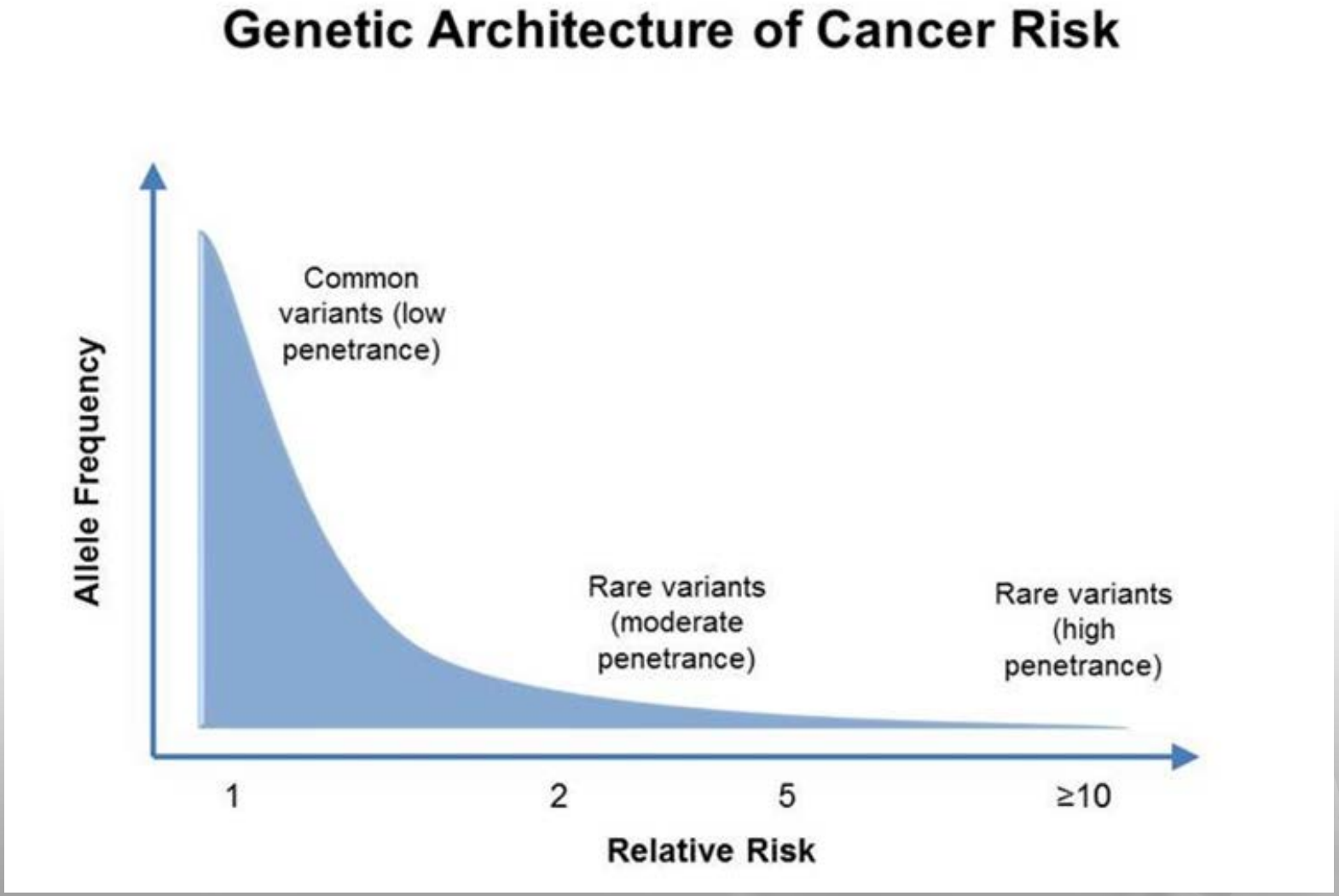
- Family members may derive benefit from newborn screening even if there is little to no benefit for the newborn
  - Facilitate diagnostic assessments
  - Inform future reproduction decisions
  - Prepare for care requirements of the child
- Residual dried blood spots can be stored for future uses
  - Policies for the disposition of dried blood spots and research use vary
- Exploration of next generation genome technologies (i.e., whole genome sequencing) for newborn screening

Interdisciplinary Collaboration to Improve Patient Outcomes

# Genetic and Genomic Influences Across the Healthcare Continuum




Calzone, et al. (2013). Relevance of genomics to healthcare and nursing practice. Journal of Nursing Scholarship, 45, 1-2.




PDQ (2018). Genetics of Breast and Ovarian Cancer. Figure 4. https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq#section/_2730

# Risk Assessment

- More than 55 hereditary cancer syndromes have been identified
- The most common cancer syndromes are those associated with breast, ovarian, and gastrointestinal cancers
  - Tumor features at diagnosis are now being used as an indication for genetic assessment
- Risk assessment also performed in other healthcare arenas such as cardiovascular diseases
- Germline susceptibility gene testing is available
  - Relevant to individuals whose disease management may be altered
  - At-risk family members

# Family History

| | In the prior three months nurses seeing patients who RARELY OR NEVER assessed a family history | AGREED OR STRONGLY AGREED that family history taking should be a key component of nursing care |
|---|---|---|
| NNWFS | 67%, (n=288/510) | 84% (n=369/442) |
| HOD | 58% (n=59/102) | 91% (n=219/242) |
| MINC | 65% (n=3193/4923) | 71% (n=4204/5942) |

# Family History, MINC

| Question | %(N) |
|---|---|
| Not at all or only a little confident in deciding what family history information is needed to identify genetic susceptibility to common diseases. | 52% (n=3313/6000) |
| Not at all or only a little confident in deciding which patients would benefit from a referral for genetic counseling and possible testing. | 64% (n=3837/5962) |
| Always Collect: | |
| Relationship to the patient | 72% (n=4010/5591) |
| Age of diagnosis | 29% (n=1617/5566) |
| Maternal and paternal lineages | 53% (n=2953/5551) |
| Race or ethnic background | 33% (n=1819/5533) |

# Multi-gene (Panel) Testing

**Table 1.** Genes Analyzed In Commercially Available Multiplex Panels

| Gene | Ambry Genetics* | | | | University of Washington Laboratory Medicine† | |
|---|---|---|---|---|---|---|
| | CancerNext | BreastNext | ColoNext | OvaNext | BROCA | ColoSeq |
| *APC* | ● | | ● | | ● | ● |
| *ATM* | ● | ● | | ● | ● | |
| *ATR* | | | | | ● | |
| *BABAM1* | | | | | ● | |
| *BAP1* | | | | | ● | |
| *BARD1* | ● | ● | | ● | ● | |
| *BMPR1A* | | | ● | | ● | |
| *BRIP1* | ● | ● | | ● | ● | |
| *CDH1* | ● | ● | ● | ● | ● | ● |
| *CDK4* | | | | | ● | |
| *CDKN2A* | | | | | ● | |
| *CHEK1* | | | | | ● | |
| *CHEK2* | ● | ● | ● | ● | ● | |
| *FAM175A/Abraxas* | | | | | ● | |
| *MLH1* | ● | | ● | ● | ● | ● |
| *MRE11A* | ● | ● | | ● | ● | |
| *MSH2*-positive *EPCAM* | ● | | ● | ● | ● | ● |
| *MSH6* | ● | | ● | ● | ● | ● |
| *MUTYH* | ● | ● | ● | ● | ● | ● |
| *NBN* | ● | ● | | ● | ● | |
| *PALB2* | ● | ● | | ● | ● | |
| *PMS2* | ● | | ● | ● | ● | ● |
| *PRSS1* | | | | | ● | |
| *PTEN* | ● | ● | ● | ● | ● | ● |
| *RAD50* | ● | ● | | ● | ● | |
| *RAD51* | | | | | ● | |
| *RAD51B* | | | | | ● | |
| *RAD51C* | ● | ● | | ● | ● | |
| *RAD51D* | | | | | ● | |
| *RBBP8* | | | | | ● | |
| *RET* | | | | | ● | |
| *SMAD4* | ● | | ● | | ● | |
| *STK11* | ● | ● | ● | ● | ● | ● |
| *TP53* | ● | ● | ● | ● | ● | ● |
| *TP53BP1* | | | | | ● | |
| *UIMC1* | | | | | ● | |
| *VHL* | | | | | ● | |
| *XRCC2* | | | | | ● | |
| *XRCC3* | | | | | ● | |

*Aliso Viejo, CA.
†Seattle, WA.

Domchek et al. (2013). Multiplex genetic testing for cancer susceptibility: Out on the high wire without at net. JCO, 31, 1267-70.

# Outcomes of Multi-Gene Panel Testing

- No variants
- Benign or likely benign variant(s)
- Variant(s) of Uncertain Significant
- Pathogenic or Likely Pathogenic variant(s) in a high-penetrance gene
  - concordant with the existing personal/family history
  - discordant with the existing personal/family history
- Pathogenic or Likely Pathogenic variant(s) in a moderate-penetrance gene
- Pathogenic or Likely Pathogenic variant(s) in a gene with uncertain cancer risks and/or cancer associations

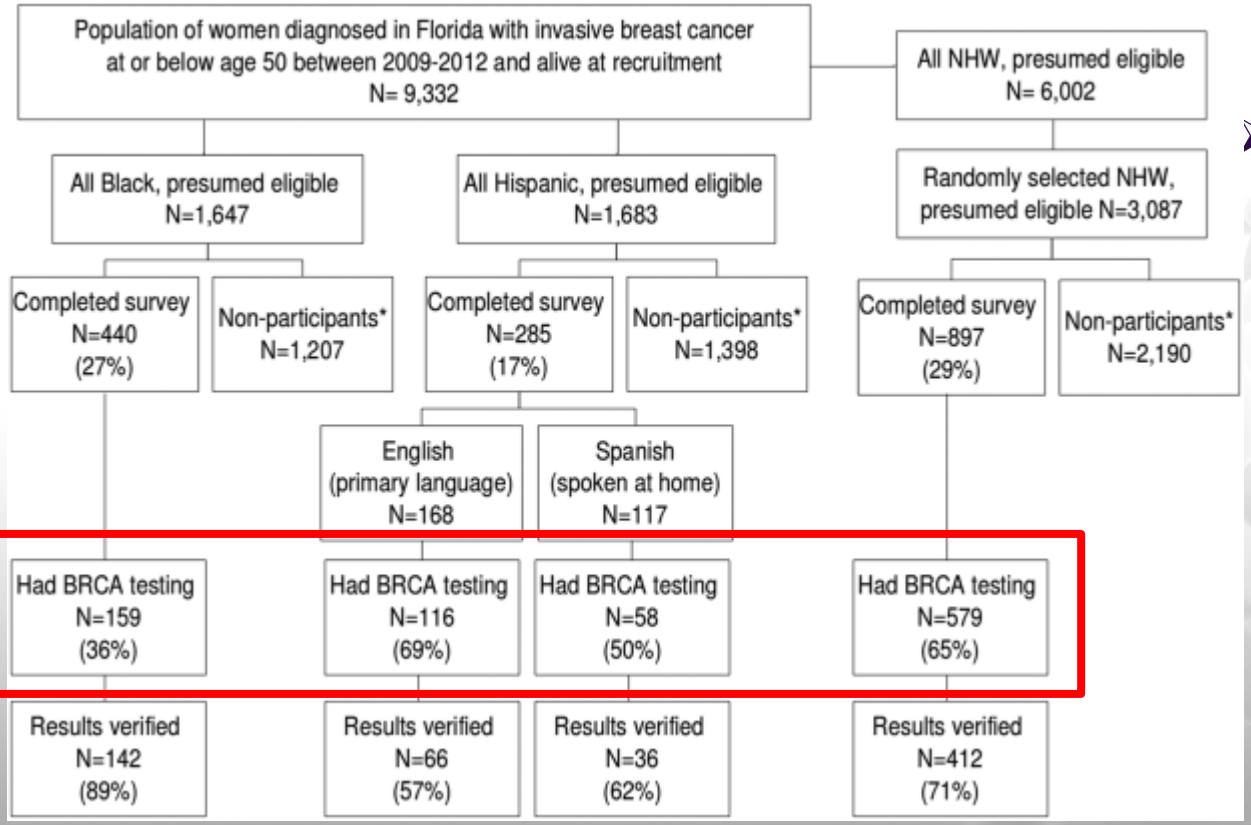
# Conflicting Genetic Test Interpretations

- 1,191 individuals tested for inherited cancer susceptibility joined PROMPT study
- 518 with 603 genetic variants had a result from more than one laboratory
  - 221 (37%) variant of uncertain significance
  - 191 (32%) as pathogenic
  - 34 (6%) as benign
  - 155 (26%) interpretation differed among reporting laboratories
    - Entire study set 56/518 (11%) had a variant with conflicting interpretations ranging from pathogenic/likely pathogenic to VUS

Balmana et al. (2016). Conflicting interpretation of genetic variants and cancer risk by commercial laboratories as assessed by the prospective registry of multiplex testing. JCO, 34, 4071-4078

# Racial Disparities in Genetic Testing

Figure 1




- Undergoing testing was associated with having a health care provider discuss testing OR 7.9

**Cancer**
9 FEB 2017 DOI: 10.1002/cncr.30621 **Racial disparities in *BRCA* testing and cancer risk management across a population-based sample of young breast cancer survivors**
http://onlinelibrary.wiley.com/doi/10.1002/cncr.30621/full#cncr30621-fig-0001

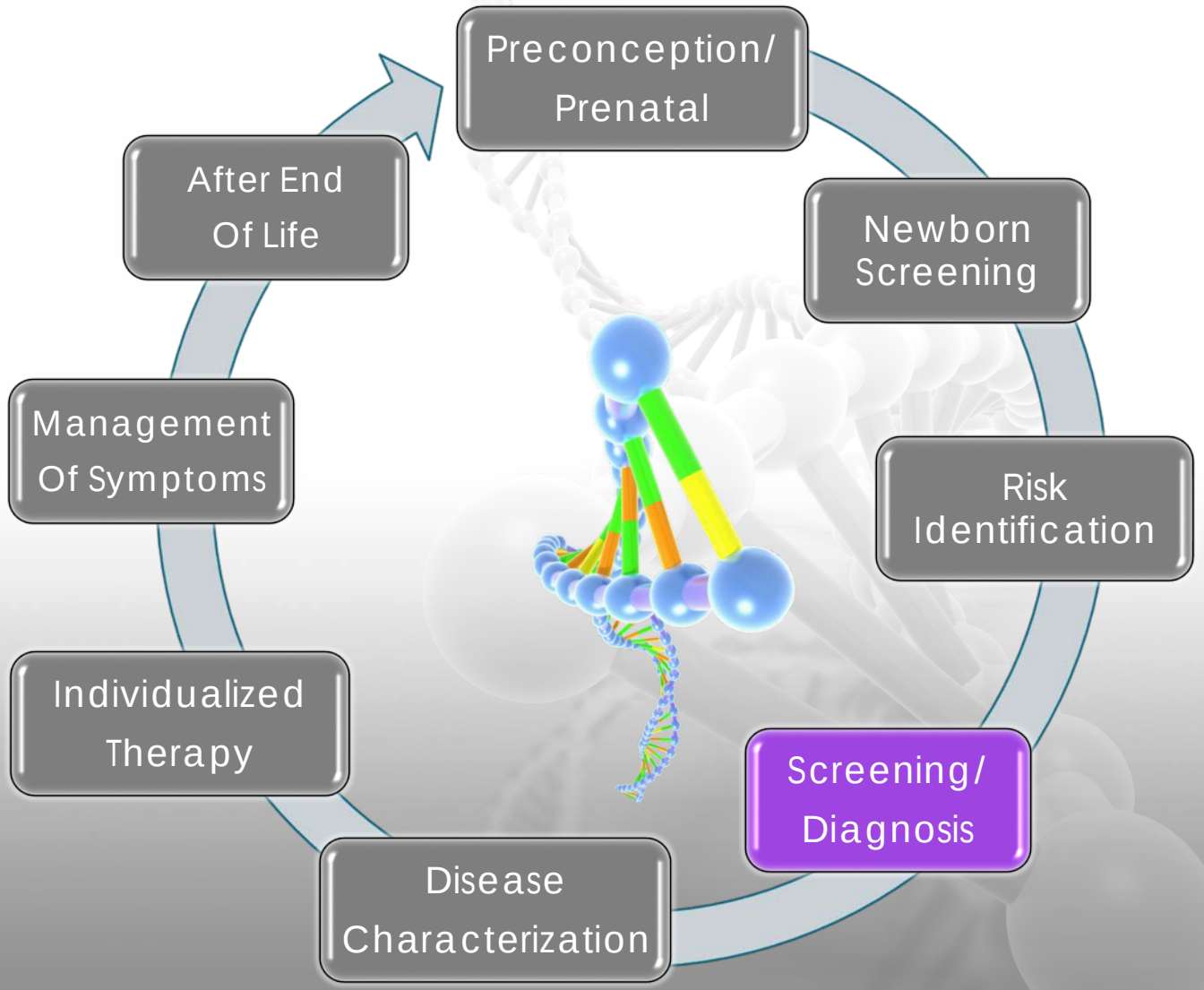
# Family History in Nursing Practice


**"It's one of those times in your life that you are grateful you had the knowledge."**

Quote from:
Barbara Ganster, RN, BSN
Breast Cancer Case Manager
National Naval Medical Center

Interdisciplinary Collaboration to Improve Health Outcomes

# Genetic and Genomic Influences Across the Healthcare Continuum




Calzone, et al. (2013). Relevance of genomics to healthcare and nursing practice. Journal of Nursing Scholarship, 45, 1-2.

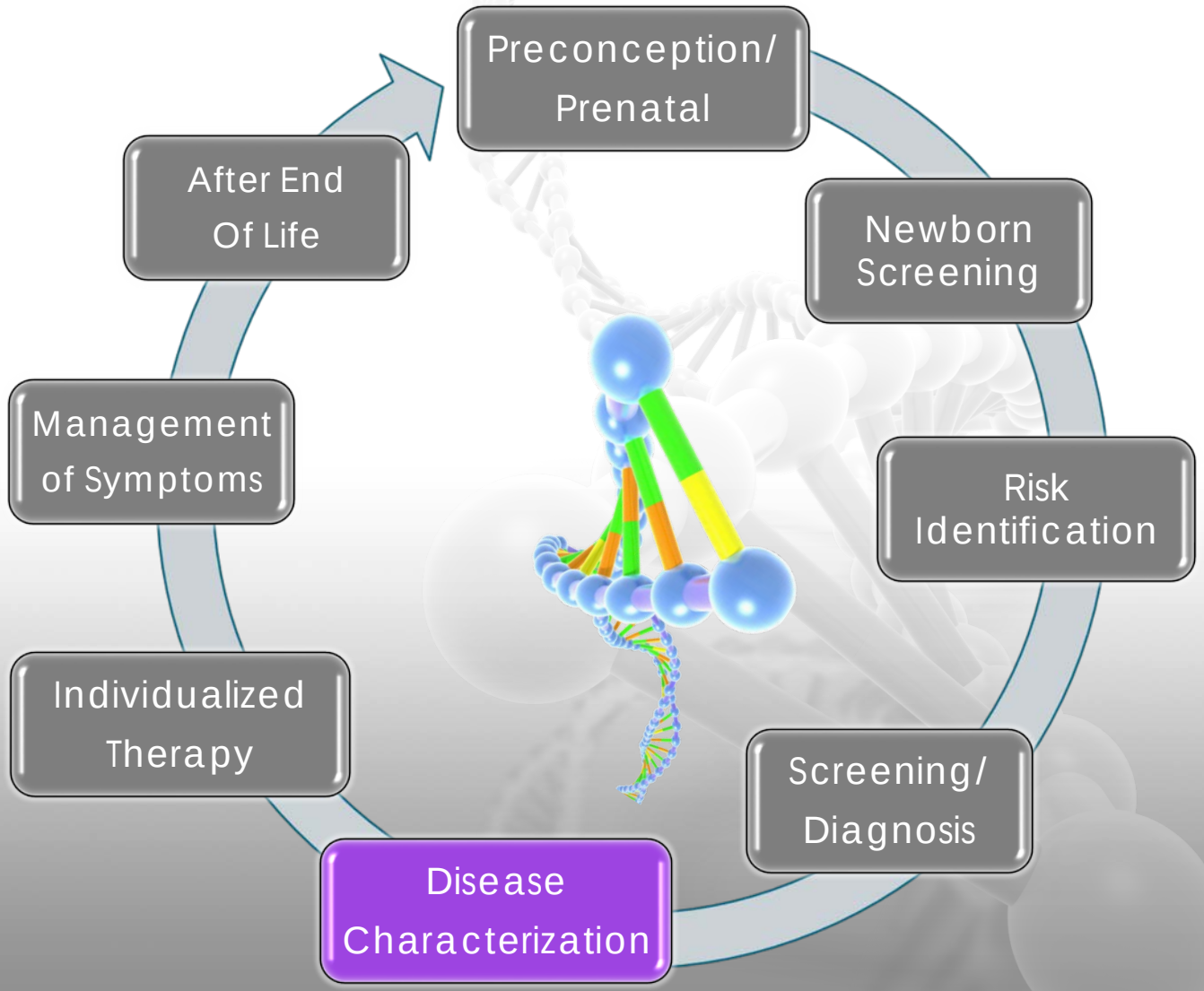
# Screening

- Genetic information is being used to personalize health screening recommendations
- SNP test results are being studied as a means to increase the specificity of risk calculation models (i.e. Gail model for breast cancer risk)
- Screening tests that include DNA analysis are being developed such as the multi-target stool DNA test, a less invasive means to screen for colon polyps or cancer
  - Approved by FDA 2014

Imperiale, T. et al. (2014). Multi-target stool DNA testing for colorectal-cancer screening. NEJM, 370,1287-97
Heigh et al. (2014). Detection of colorectal serrated polyps by stool DNA testing: comparison with fecal immunochemical testing for occult blood (FIT). PLoSOne, 9, 9(1)e85659

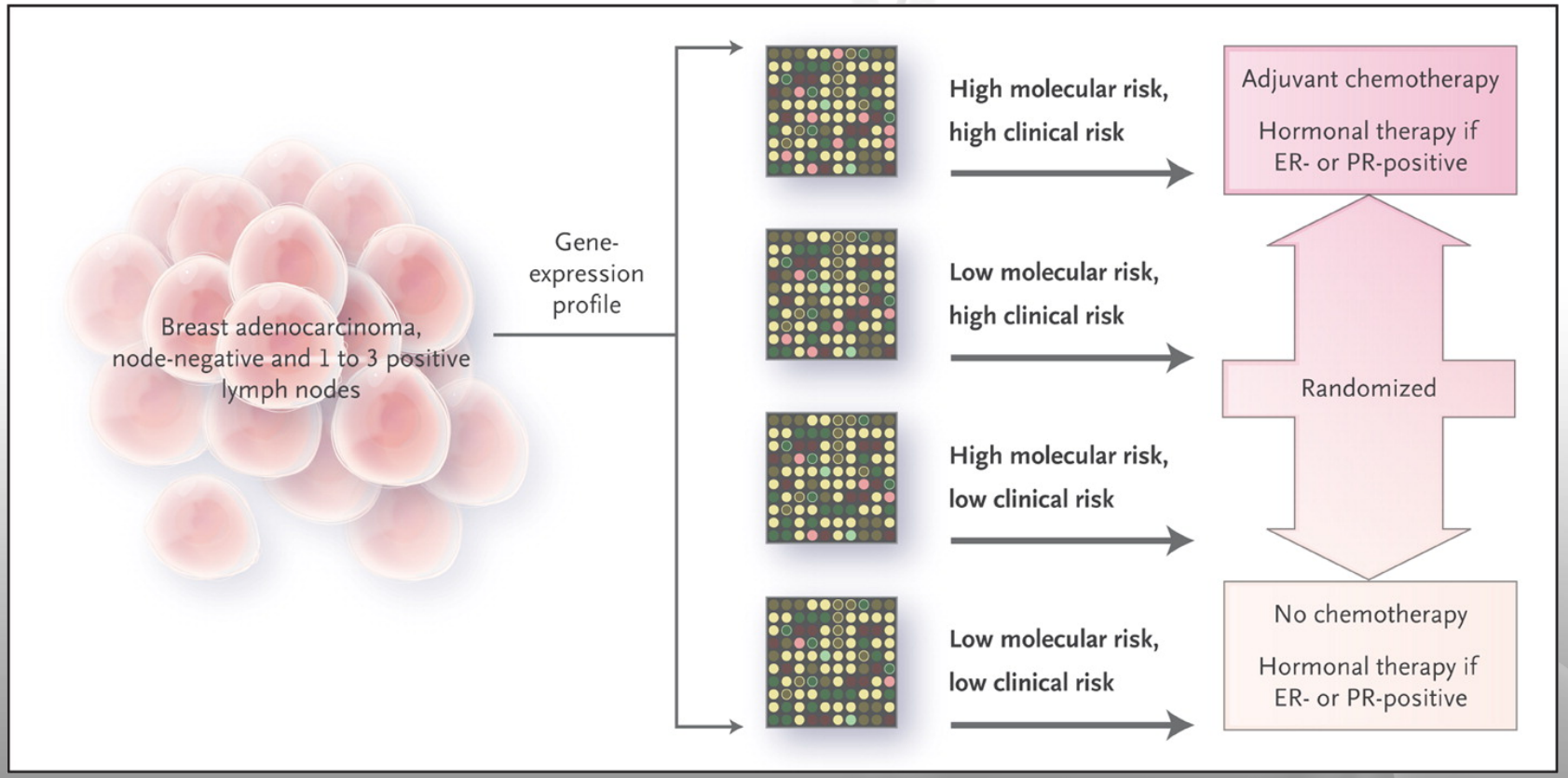
Interdisciplinary Collaboration to Improve Health Outcomes

# Genetic and Genomic Influences Across the Healthcare Continuum



# Diagnosis/Prognosis

- Establish an accurate diagnosis
- Tumor profiling is being used to identify recurrence risk to guide adjuvant therapy

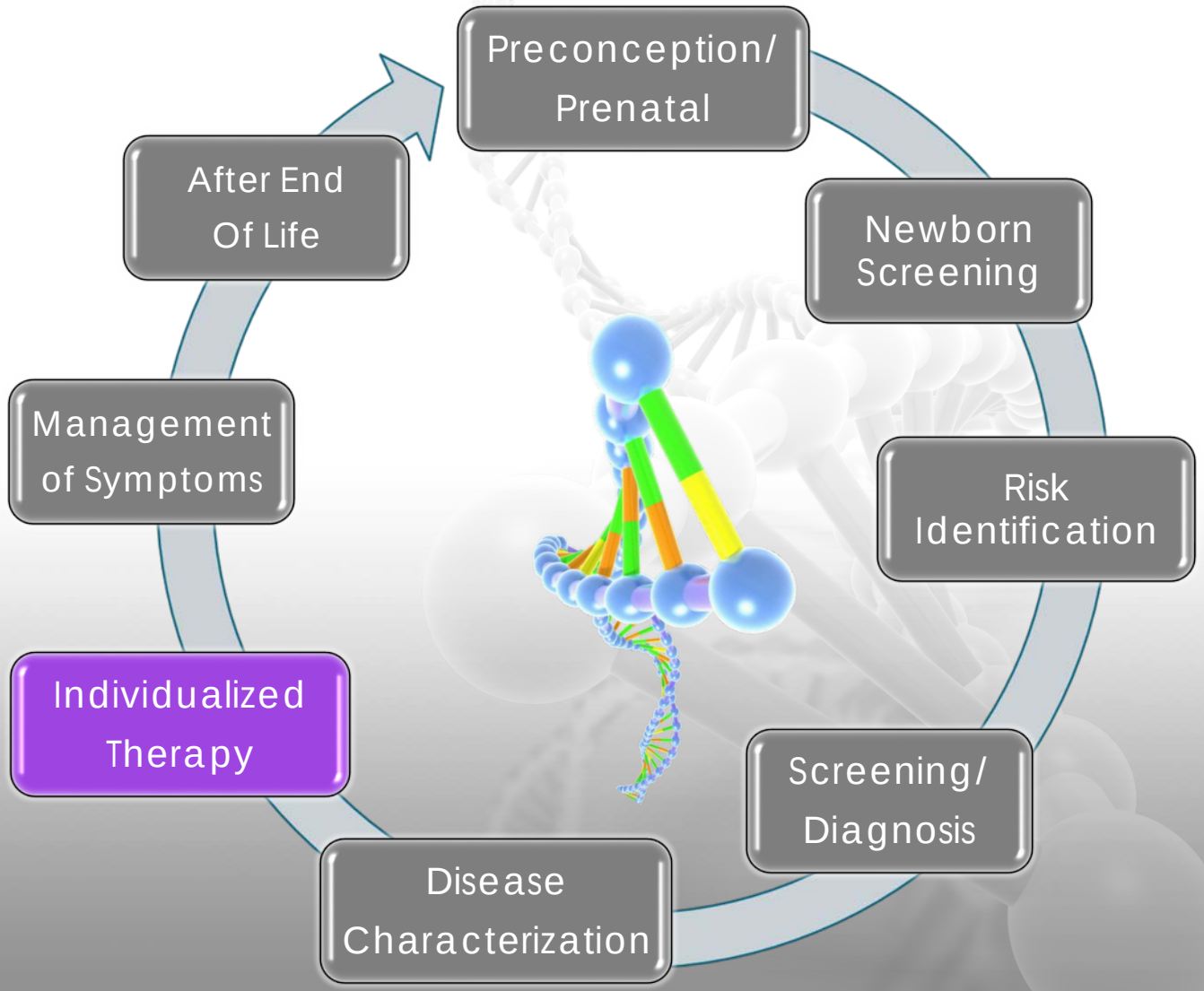



McDermott et al. (2011). Genomics and the continuum of cancer care, NEJM, 364, 350-360.

The NEW ENGLAND JOURNAL of MEDICINE

Interdisciplinary Collaboration to Improve Health Outcomes

# Genetic and Genomic Influences Across the Healthcare Continuum



# Evolution of Knudson Two Hit Hypothesis

TIMELINE

## Two genetic hits (more or less) to cancer

*Alfred G. Knudson*

Most cancers have many chromosomal abnormalities, both in number and in structure, whereas some show only a single aberration. In the era before molecular biology, cancer researchers, studying both human and animal cancers, proposed that a small number of events was needed for carcinogenesis. Evidence from the recent molecular era also indicates that cancers can arise from small numbers of events that affect common cell birth and death processes.

We are now very familiar with the concept that cancer occurs as a consequence of several somatic mutations, but how did this concept first arise? The idea that cancer is a genetic disease of somatic cells — proposed by Theodor Boveri in 1914 (REF. 1) — was prompted by previous observations of aberrant mitoses by David von Hansemann[2], and by Boveri's own interest in centrosomes and their abnormalities during development (see TIMELINE). Boveri even suggested some consequences of abnormal chromosome numbers, anticipating the contemporary era of tumour-suppressor genes and oncogenes (BOX 1)[3]. The term 'somatic mutation' was first applied to cancer by Ernest Tyzzer[4], who observed that tumours sequentially transplanted in mice developed an ever-broadening host specificity among recipients from different inbred strains. Concrete support for the genetic concept came from Hermann J. Muller's[5] discovery that ionizing radiation, already known to be carcinogenic, is mutagenic. The long latent period between exposure to such radiation and the appearance of most of the inducible cancers further indicated that more than one mutation per cell must be involved[6]. Subsequently, the high incidence of skin





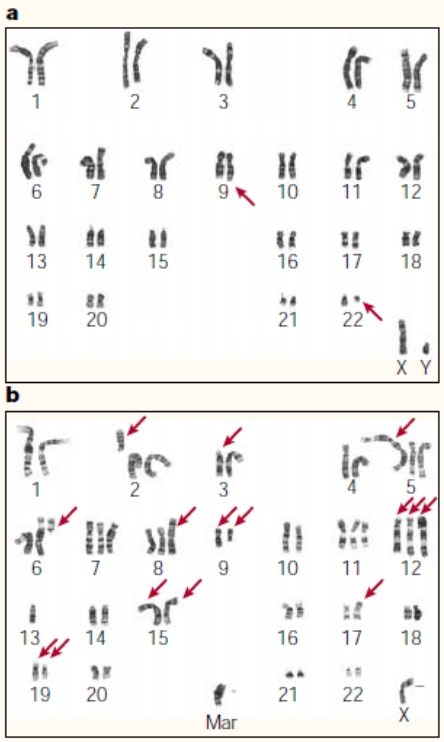
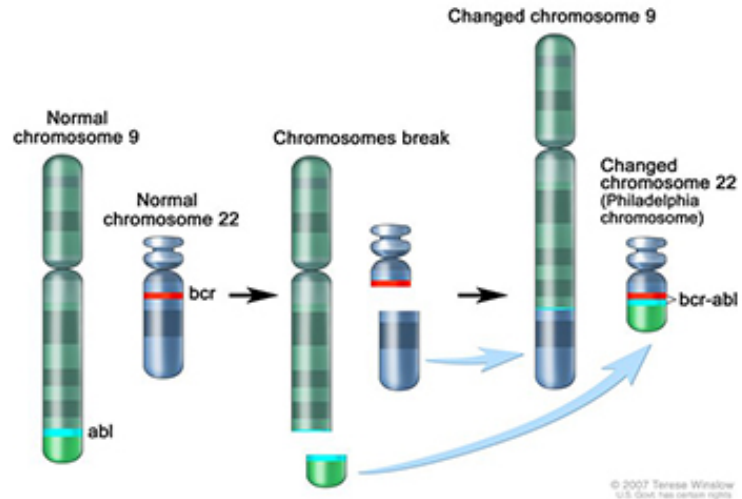



Figure 2 | **A comparison of karyotypes. a** | Chronic myelogenous leukaemia, showing the typical 9;22 translocation and an otherwise normal karyotype. **b** | Non-small-cell carcinoma of the lung, showing abnormalities of both number and structure. The arrows indicate aberrant chromosomes.

Knudson, A.G. (2001). Two genetic hits (more or less) to cancer. Nature Reviews, 1,157-62.

# Chronic Myelogenous Leukemia (CML)




CML is caused by one translocation that creates a singular mutation, the BCR-ABL fusion gene or Philadelphia chromosome.

https://www.cancer.gov/research/progress/discovery/gleevec

# Targeted Therapy and CML

- 1970's Philadelphia Chromosome
- 1980's fusion protein BCR-ABL
- 1986 discovered this protein produced an abnormal protein, a tyrosine kinase
  - Stimulates uncontrolled cell growth in WBCs
- 1990's Imatinib was developed
- 1998 first in human studies

# Scope of Targeted Therapies

- Hormones
- Signal transduction inhibitors
- Gene expression modulators
- Apoptosis inducers
- Angiogenesis inhibitors
- Immunotherapies
- Monoclonal antibodies that deliver toxic molecules
- Vaccines

# Driver versus Passenger Variants

## Driver

- Growth advantage on the cell
- Does not need to be required for maintenance of the final cancer (although it often is) but it must have been selected at some point along the lineage of cancer

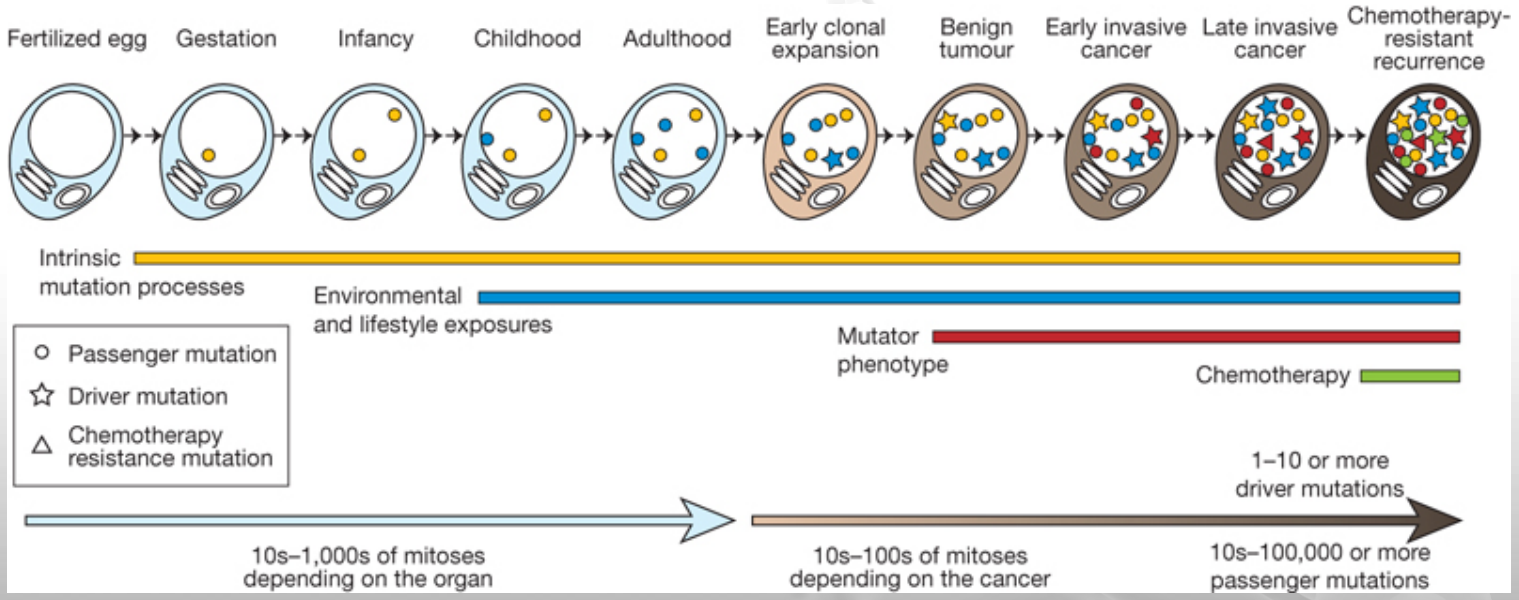
## Passenger

- Does not have growth advantage and has therefore not contributed to cancer development
  - a cell that acquires a driver variant will already have biologically inert somatic variants within its genome

Stratton, M.R. et al. (2009). The cancer genomic. *Nature* **458**, 719-724

# Somatic Variants and Cancer

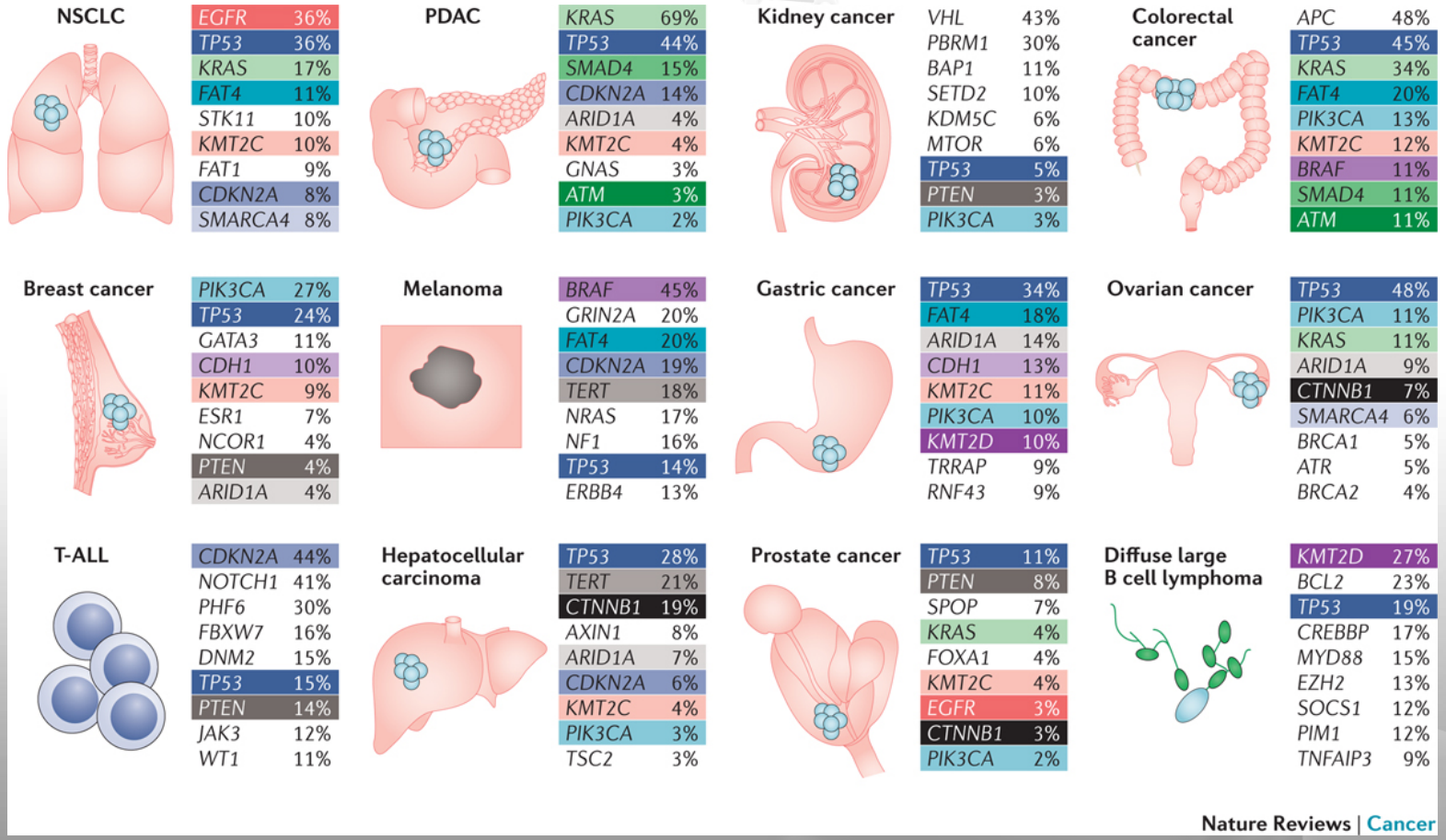
The lineage of mitotic cell divisions from the fertilized egg to a single cell within a cancer showing the timing of the somatic mutations acquired by the cancer cell and the processes that contribute to them.




MR Stratton *et al. Nature* **458**, 719-724 (2009) doi:10.1038/nature07943

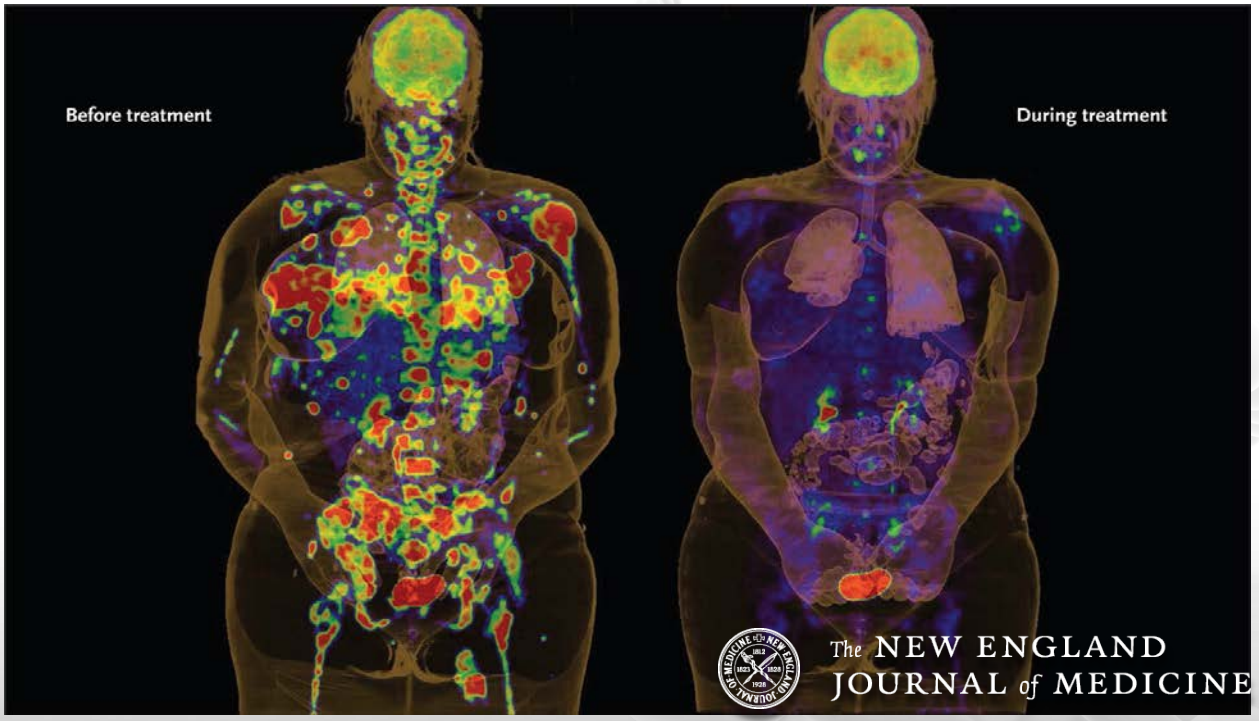
nature

# Top Nine Mutations Occurring in Common Cancers




Schneider, et al. (2017). Tissue-specific tumorigenesis: context matters. Nature Reviews Cancer, 17, 239-253.

# Cancer Tumor Profiling




- Basket trials hypotheses
  - The presence of a molecular marker predicts response to a targeted therapy independent of tumor histology.



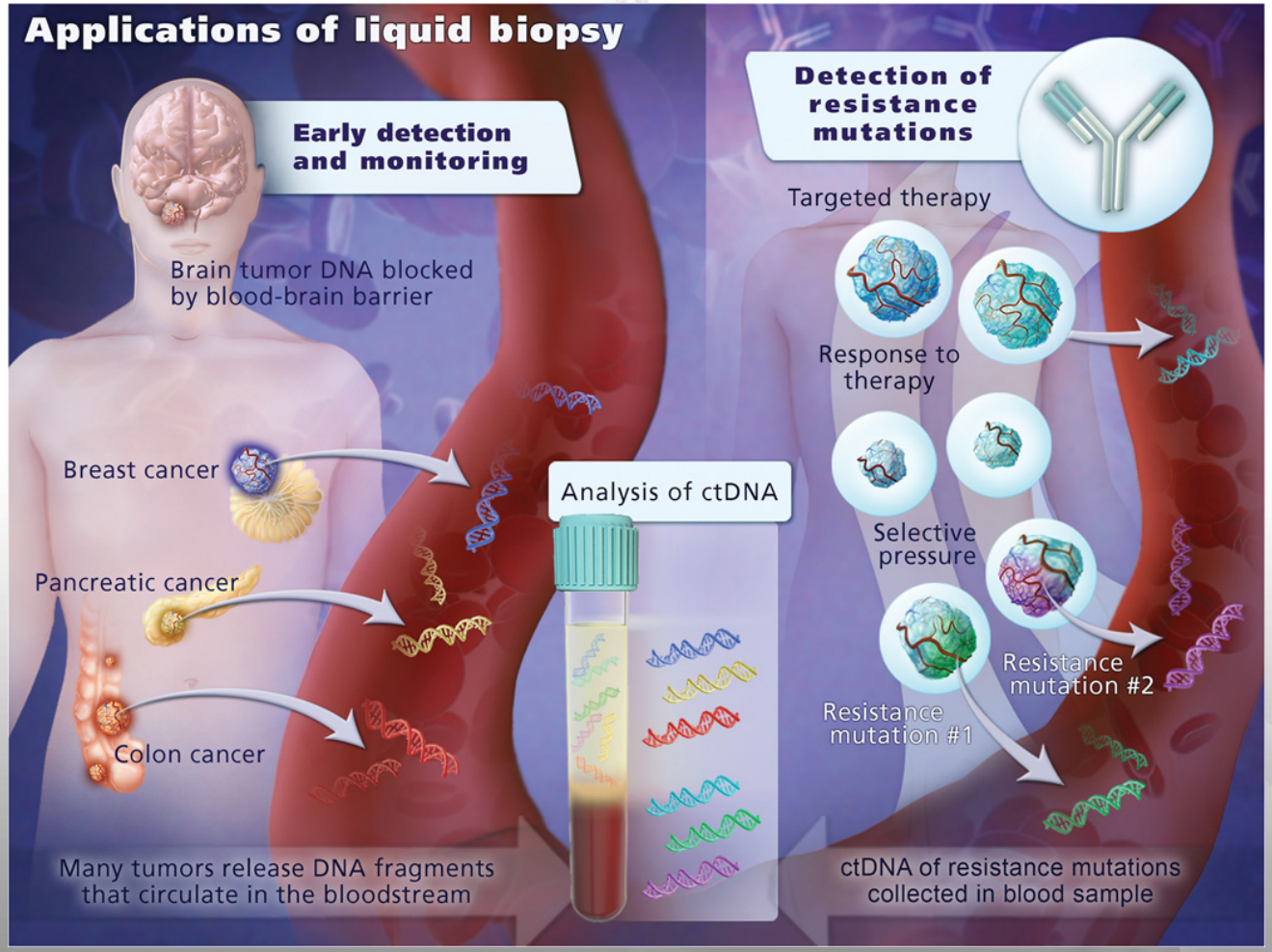
McDermott et al. (2011). Genomics and the continuum of cancer care, NEJM, 364, 350-360.
Redig A. et al. (2015). Basket trials and the evolution of clinical trial design in an era of genomic medicine. JCO, 33, 975-7.

# Somatic Testing and Germline Incidental Findings

- 1566 patients MSK-IMPACT trial
- Pathogenic germline variants identified in 246/1566 patients (15.7%)
  - 198 individuals with mutations in cancer susceptibility genes
- Germline cancer susceptibility genes were concordant with the individual's cancer type in 81/198 cases (40.9%)
- Mutations in non-cancer-related Mendelian disease genes were seen in 55/1566 cases (3.5%)

Catenacci DV, et al. (2015). Tumor genome analysis includes germline genome: Are we ready for surprises? Int J Cancer, 136:1559-67.
Raymond VM, et al. (2016). Germline Findings in Tumor-Only Sequencing: Points to Consider for Clinicians and Laboratories. JNCI, 108.
Schrader KA, et al. (2016). Germline Variants in Targeted Tumor Sequencing Using Matched Normal DNA. JAMA oncology, 2, 104-11.

# Circulating Tumor DNA

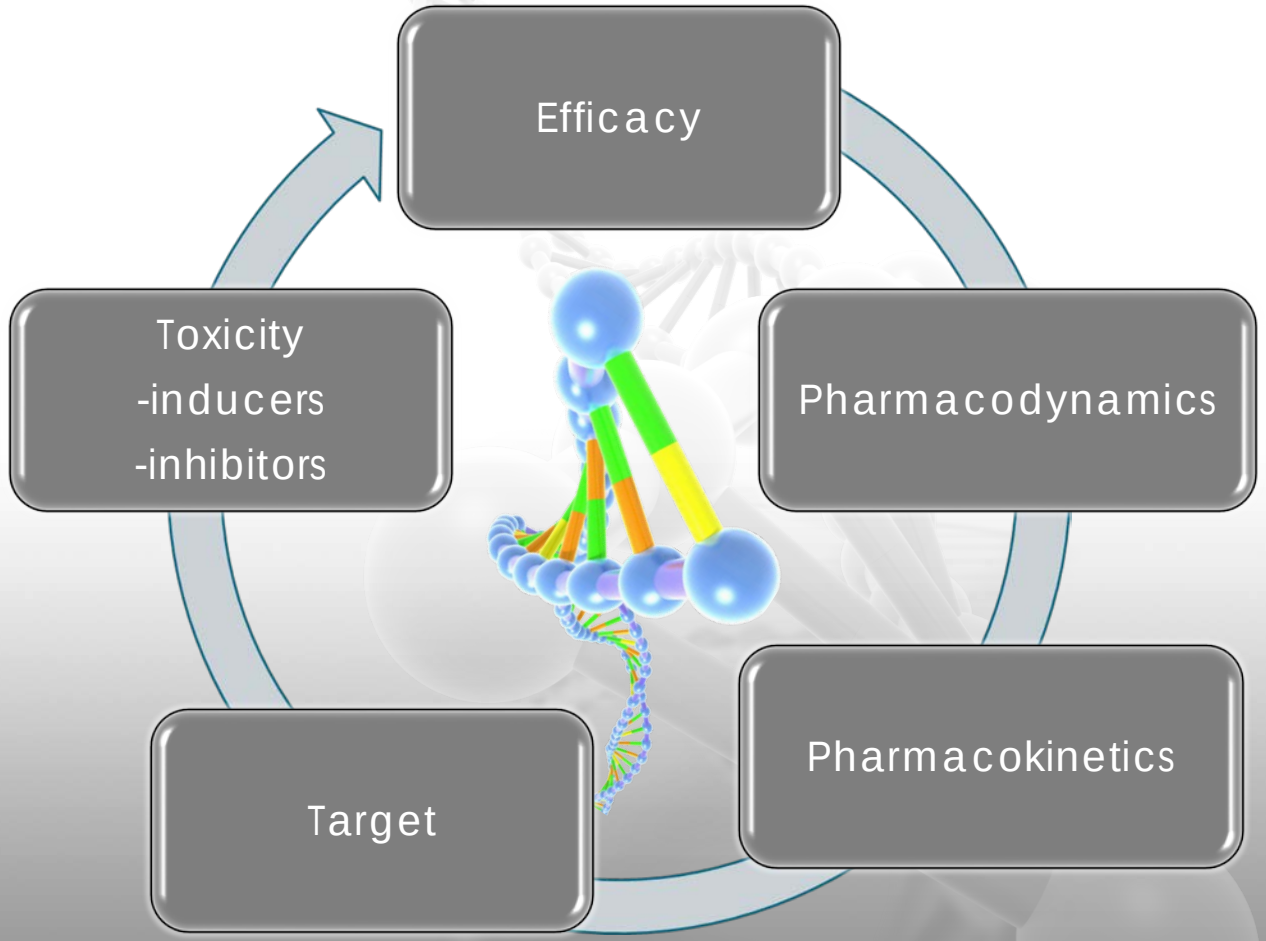



Chetan Bettegowda et al., Sci Transl Med 2014;6:224ra24

Published by AAAS

Science Translational Medicine AAAS

# Pharmacogenomic Influences




PK = absorption, distribution, metabolism and excretion
PD = mechanism of action, drug concentration and effect

# Polymorphisms and Phenotype

- **UM-Ultrarapid Metabolizer**
  - Unusually high activity of a drug metabolizing enzyme (DME) or drug transport protein (DTP)
  - Limited response to recommended doses
- **EM-Extensive Metabolizer**
  - Wild-type (normal activity) form of a DME or DTP
  - Expected efficacy at recommended doses
- **IM-Intermediate Metabolizer**
  - Reduced activity of a DME or DTP
  - Some decreased efficacy at recommended doses
- **PM-Poor Metabolizer**
  - Very low or no activity of a DME or DTP
  - Increased toxicity
  - Decreased efficacy at recommended doses

Katz et al. (2008). Defining drug disposition determinants: A pharmacogenetic–pharmacokinetic strategy. Nature Reviews Drug Discovery, 7, 293-305.

# FDA Table of Pharmacogenomic Biomarkers in Drug Labeling

- Drug labeling may contain information:
  - Drug exposure and clinical response variability
  - Risk for adverse events
  - Genotype-specific dosing
  - Mechanisms of drug action
  - Polymorphic drug target and disposition genes
- >200 drugs listed in this table
  - Analgesia, cardiology, endocrinology, gastroenterology, hematology, in-born errors of metabolism, neurology, oncology, infectious disease, psychiatry, rheumatology, toxicology, transplant

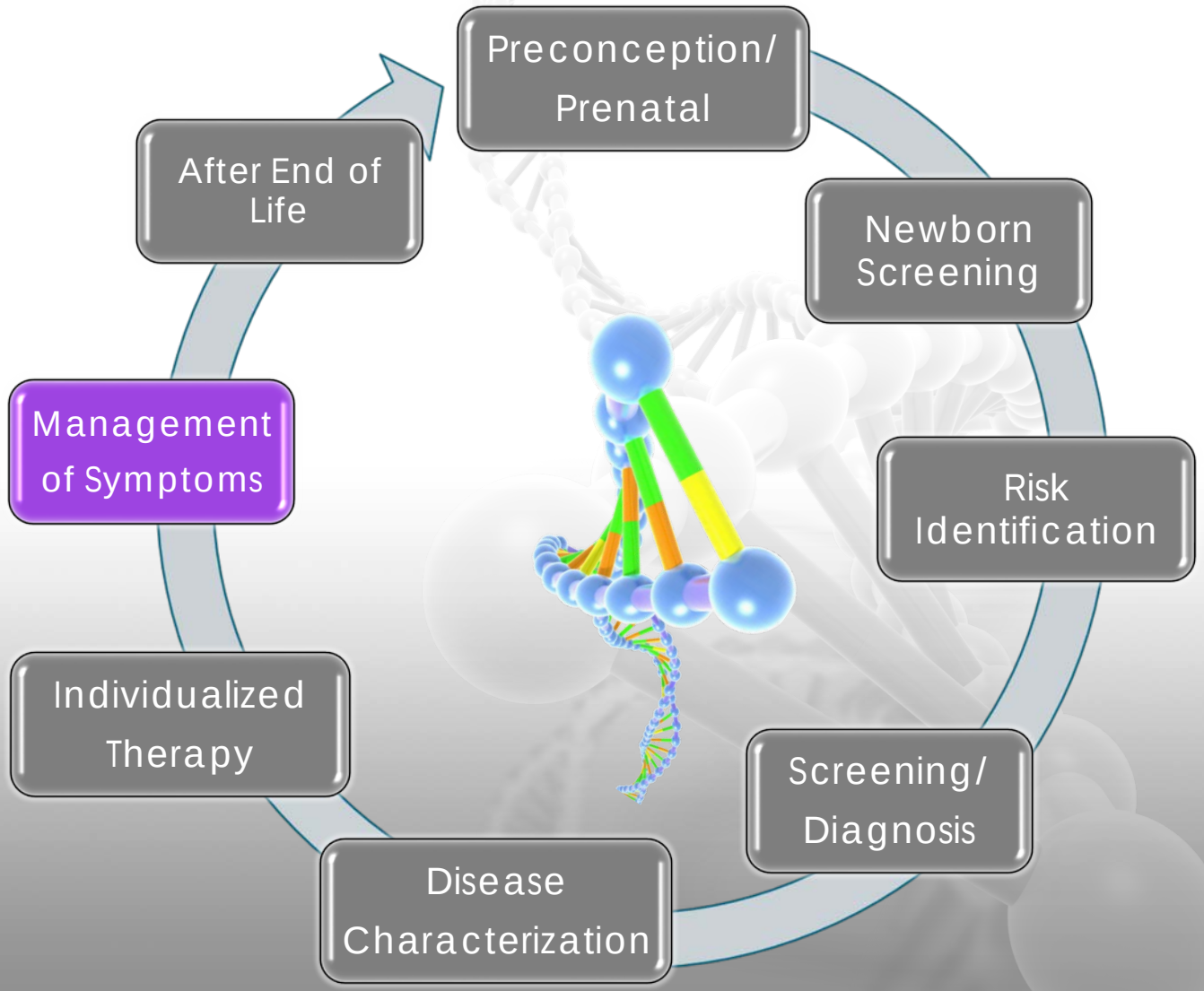
http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

# Pharmacogenomic Considerations

- Pre-emptive versus reactive testing
- Electronic Health Record point of care clinical decision support infrastructure
- Ready access to PharmGKB and Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines
  - https://www.pharmgkb.org/

Interdisciplinary Collaboration to Improve Health Outcomes

# Genetic and Genomic Influences Across the Healthcare Continuum

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24

# Polymorphisms and Phenotype

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Katz et al. (2008). Defining drug disposition determinants: A pharmacogenetic–pharmacokinetic strategy. Nature Reviews Drug Discovery, 7, 293-305.

# Symptom Management

- Priority area of nursing research is the study of the genetic influences of symptom clusters
- Pharmacogenomics
  - Inhibitors and/or Inducers
    - Implications for:
      - Medications used for other health conditions
      - Selecting medications to control
      - Use of over the counter medications like St. Johns' Wort
      - Consumption of certain foods or supplements like grapefruit/grapefruit juice

# Inhibitors and Inducers

- **Inhibitors**
  - Reduce the drug metabolizing enzyme or drug transport protein
- **Inducers**
  - Increase the drug metabolizing enzyme or drug transport protein

# Indiana University Drug Interaction Table

## P450 Drug Interaction Table

### SUBSTRATES

| 1A2 | 2B6 | 2C8 | 2C9 | 2C19 | 2D6 | 2E1 | 3A4,5,7 |
|---|---|---|---|---|---|---|---|
| amitriptyline | artemisinin | amodiaquine2 | **NSAIDs:** | **PPIs:** | tamoxifen: | **Anesthetics:** | **Macrolide antibiotics:** |
| caffeine2 | bupropion1 | cerivastatin | diclofenac1 | esomeprazole | **TAMOXIFEN GUIDE** | enflurane | clarithromycin |
| clomipramine | cyclophosphamide | paclitaxel | ibuprofen | lansoprazole | | halothane | erythromycin2 (not 3A5) |
| clozapine | efavirenz1 | repaglinide | lornoxicam | omeprazole2 | **Beta Blockers:** | isoflurane | NOT azithromycin |
| cyclobenzaprine | ifosphamide | sorafenib | meloxicam | pantoprazole | carvedilol | methoxyflurane | telithromycin |
| duloxetine | ketamine | torsemide | S-naproxen→Nor | | S-metoprolol | sevoflurane | |
| estradiol | meperidine | | piroxicam | **Anti-epileptics:** | propafenone | | **Anti-arrhythmics:** |
| fluvoxamine | methadone | | suprofen | diazepam→Nor | timolol | acetaminophen→NAPQI | quinidine→3-OH (not 3A5) |
| haloperidol | nevirapine | | | phenytoin(O) | | aniline2 | |
| imipramine N-DeMe | propafol | | **Oral Hypoglycemic Agents:** | S-mephenytoin1 | **Antidepressants:** | benzene | |
| mexiletine | selegiline | | tolbutamide1 | phenobarbitone | amitriptyline | chlorzoxazone1 | **Benzodiazepines:** |
| nabumetone | sorafenib | | glipizide | | clomipramine | ethanol | alprazolam |
| naproxen | | | | amitriptyline | desipramine | N,N-dimethylformamide | diazepam→3OH |
| olanzapine | | | **Angiotensin II Blockers:** | carisoprodol | fluoxetine | theophylline→8-OH | midazolam1 |
| ondansetron | | | losartan | citalopram | imipramine | | triazolam2 |
| phenacetin1→ acetaminophen →NAPQI | | | irbesartan | chloramphenicol | paroxetine | | **Immune Modulators:** |
| propranolol | | | | clomipramine | venlafaxine | | cyclosporine |
| riluzole | | | **Sulfonylureas:** | clopidogrel | | | tacrolimus (FK506) |
| ropivacaine | | | glyburide | cyclophosphamide | **Antipsychotics:** | | |
| tacrine2 | | | glibenclamide | hexobarbital | haloperidol | | **HIV Antivirals:** |
| theophylline2 | | | glipizide | imipramine N-DeME | perphenazine | | indinavir |
| tizanidine | | | glimepiride | indomethacin | risperidone→9-OH | | nelfinavir |
| triamterene | | | tolbutamide | labetalol | thioridazine | | ritonavir |
| verapamil | | | | R-mephobarbital | zuclopenthixol | | saquinavir |
| (R)warfarin | | | amitriptyline | moclobemide | | | |
| zileuton | | | celecoxib | nelfinavir | alprenolol | | **Prokinetic:** |
| zolmitriptan | | | fluoxetine | nilutamide | amphetamine | | cisapride |
| | | | fluvastatin | primidone | aripiprazole | | |
| | | | glyburide | progesterone | atomoxetine | | **Antihistamines:** |
| | | | nateglinide | proguanil | bufuralol1 | | astemizole |
| | | | phenytoin-4-OH2 | propranolol | chlorpheniramine | | chlorpheniramine |
| | | | rosiglitazone | teniposide | chlorpromazine | | terfenadine2 |
| | | | tamoxifen | R-warfarin→8-OH | clonidine | | |
| | | | torsemide | voriconazole | codeine (→O-desMe) | | |
| | | | valproic acid | | debrisoquine2 | | |
| | | | S-warfarin1 | | dexfenfluramine | | |
| | | | zakirlukast | | dextromethorphan1 | | |
| | | | | | donepezil | | |
| | | | | | duloxetine | | |
| | | | | | encainide | | |
| | | | | | flecainide | | |
| | | | | | fluvoxamine | | |
| | | | | | lidocaine | | |
| | | | | | metoclopramide | | |
| | | | | | methoxyamphetamine | | |
| | | | | | mexiletine | | |
| | | | | | minaprine | | |
| | | | | | nebivolol | | |
| | | | | | nortriptyline | | |

http://medicine.iupui.edu/clinpharm/ddis/main-table/

# Inducers

## INDUCERS

| 1A2 | 2B6 | 2C8 | 2C9 | 2C19 | 2D6 | 2E1 | 3A4,5,7 |
|---|---|---|---|---|---|---|---|
| broccoli | artemisinin | rifampin[1] | carbamazepine | carbamazepine | dexamethasone | ethanol | HIV Antivirals: |
| brussel sprouts | carbamazepine | | nevirapine | efavirenz | rifampin | isoniazid | efavirenz |
| carbanazepine | efavirenz | | phenobarbital | norethindrone | | | nevirapine |
| char-grilled meat | nevirapine | | rifampin | NOT pentobarbital | | | |
| insulin | phenobarbital | | secobarbital | prednisone | | | barbiturates |
| methylcholanthrene[1] | phenytoin | | St. John's Wort | rifampicin[1] | | | carbamazepine |
| modafinil | rifampin | | | ritonavir | | | glucocorticoids |
| nafcillin | | | | St. John's Wort | | | modafinil |
| beta-naphthoflavone[1] | | | | | | | oxcarbazepine |
| omeprazole[1] | | | | | | | phenobarbital[2] |
| rifampin | | | | | | | phenytoin[2] |
| tobacco | | | | | | | pioglitazone |
| | | | | | | | rifabutin |
| | | | | | | | rifampin[1] |
| | | | | | | | St. John's Wort |
| | | | | | | | troglitazone[1] |

http://medicine.iupui.edu/clinpharm/ddis/main-table/

# Inhibitors

Inhibitors compete with other drugs for a particular enzyme thus affecting the optimal level of metabolism of the substrate drug which in many cases affect the individual's response to that particular medication, e.g. making it ineffective.

- A **Strong inhibitor** is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
- A **Moderate inhibitor** is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.
- A **Weak inhibitor** is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.

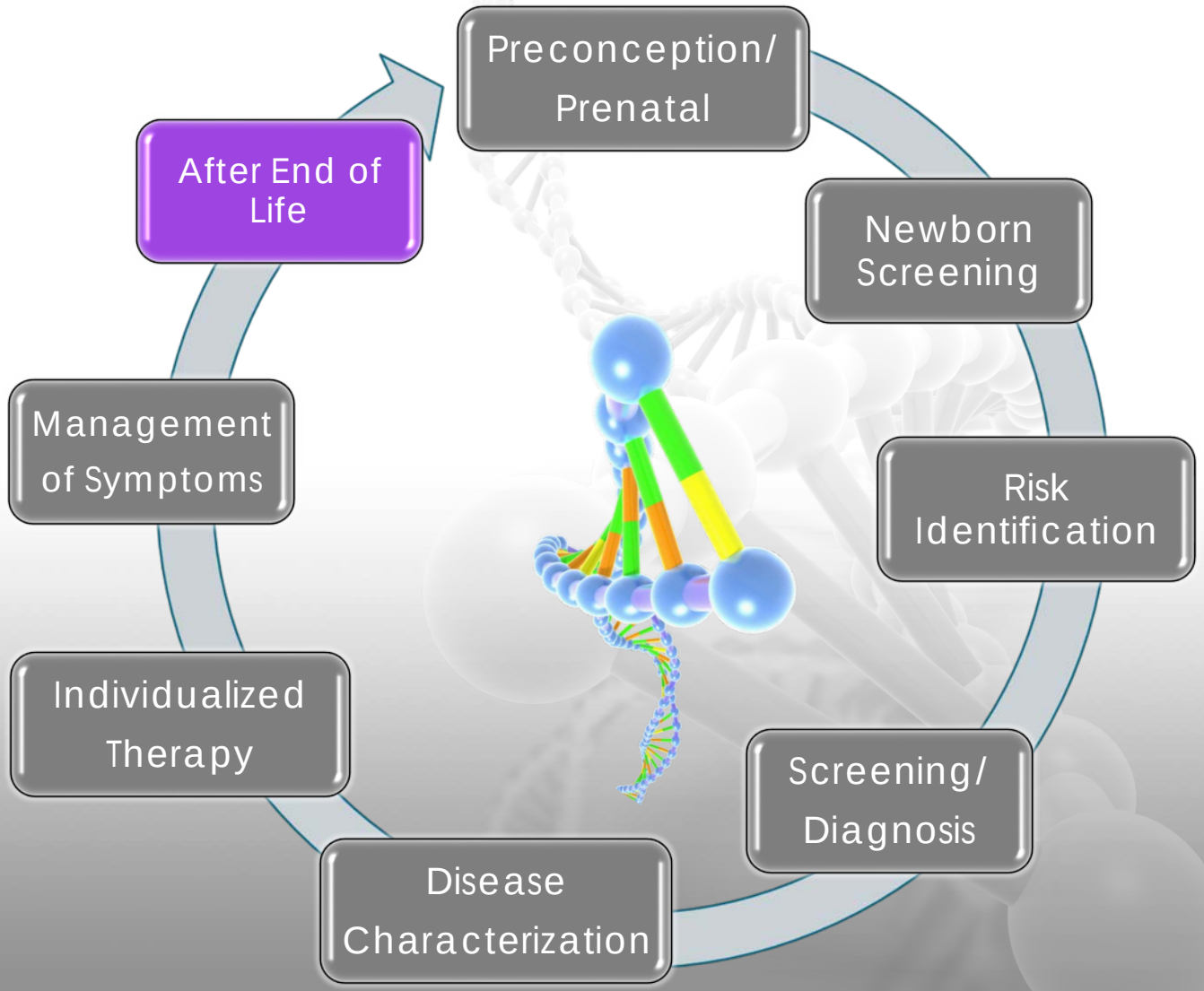
FDA preferred[1] and acceptable[2] **inhibitors** for in vitro experiments.*

| 1A2 | 2B6 | 2C8 | 2C9 | 2C19 | 2D6 | 2E1 | 3A4,5,7 |
|---|---|---|---|---|---|---|---|
| ■ fluvoxamine | clopidogrel | ■ gemfibrozil[2] | ■ fluconazole[2] | PPIs: | ■ bupropion | diethyl-dithiocarbamate[2] | HIV Antivirals: |
| ■ ciprofloxacin | thiotepa | | ■ amiodarone | esomeprazole | ■ cinacalcet | disulfiram | ■ indinavir |
| | ticlopidine[2] | | | lansoprazole | ■ fluoxetine | | ■ nelfinavir |
| ■ cimetidine | voriconazole | ■ trimethoprim[2] | efavirenz | omeprazole[2] | ■ paroxetine | | ■ ritonavir |
| | | | fenofibrate | pantoprazole | ■ quinidine[1] | | |
| amiodarone | | glitazones | fluconazole | | | | ■ clarithromycin |
| efavirenz | | montelukast[1] | fluvastatin | Other: | ■ duloxetine | | ■ itraconazole[1] |
| fluoroquinolones | | quercetin[1] | fluvoxamine[2] | chloramphenicol | ■ sertraline | | ■ ketoconazole |
| fluvoxamine | | | isoniazid | cimetidine | ■ terbinafine | | ■ nefazodone |
| furafylline[1] | | | lovastatin | felbamate | | | ■ saquinavir |
| interferon | | | metronidazole | fluoxetine | ■ amiodarone | | ■ suboxone |
| methoxsalen | | | paroxetine | fluvoxamine | ■ cimetidine | | ■ telithromycin |
| mibefradil | | | phenylbutazone | indomethacin | | | |
| ticlopidine | | | probenicid | isoniazid | celecoxib | | ■ aprepitant |
| | | | sertraline | ketoconazole | chlorpheniramine | | ■ erythromycin |
| | | | sulfamethoxazole | modafinil | chlorpromazine | | ■ fluconazole |
| | | | sulfaphenazole[1] | oral | citalopram | | ■ grapefruit juice |
| | | | teniposide | contraceptives | clemastine | | ■ verapamil[2] |
| | | | voriconazole | oxcarbazepine | clomipramine | | ■ diltiazem |
| | | | zafirlukast | probenicid | cocaine | | |
| | | | | ticlopidine2 | diphenhydramine | | ■ cimetidine |
| | | | | topiramate | doxepin | | |
| | | | | voriconazole | doxorubicin | | amiodarone |
| | | | | | escitalopram | | NOT azithromycin |
| | | | | | halofantrine | | chloramphenicol |
| | | | | | haloperidol | | boceprevir |
| | | | | | histamine H1 receptor | | ciprofloxacin |
| | | | | | antagonists | | delaviridine |
| | | | | | hydroxyzine | | diethyl- |
| | | | | | levomepromazine | | dithiocarbamate |
| | | | | | methadone | | fluvoxamine |
| | | | | | metoclopramide | | gestodene |
| | | | | | mibefradil | | |
| | | | | | midodrine | | |
| | | | | | moclobemide | | |
| | | | | | perphenazine | | |

http://medicine.iupui.edu/clinpharm/ddis/main-table/

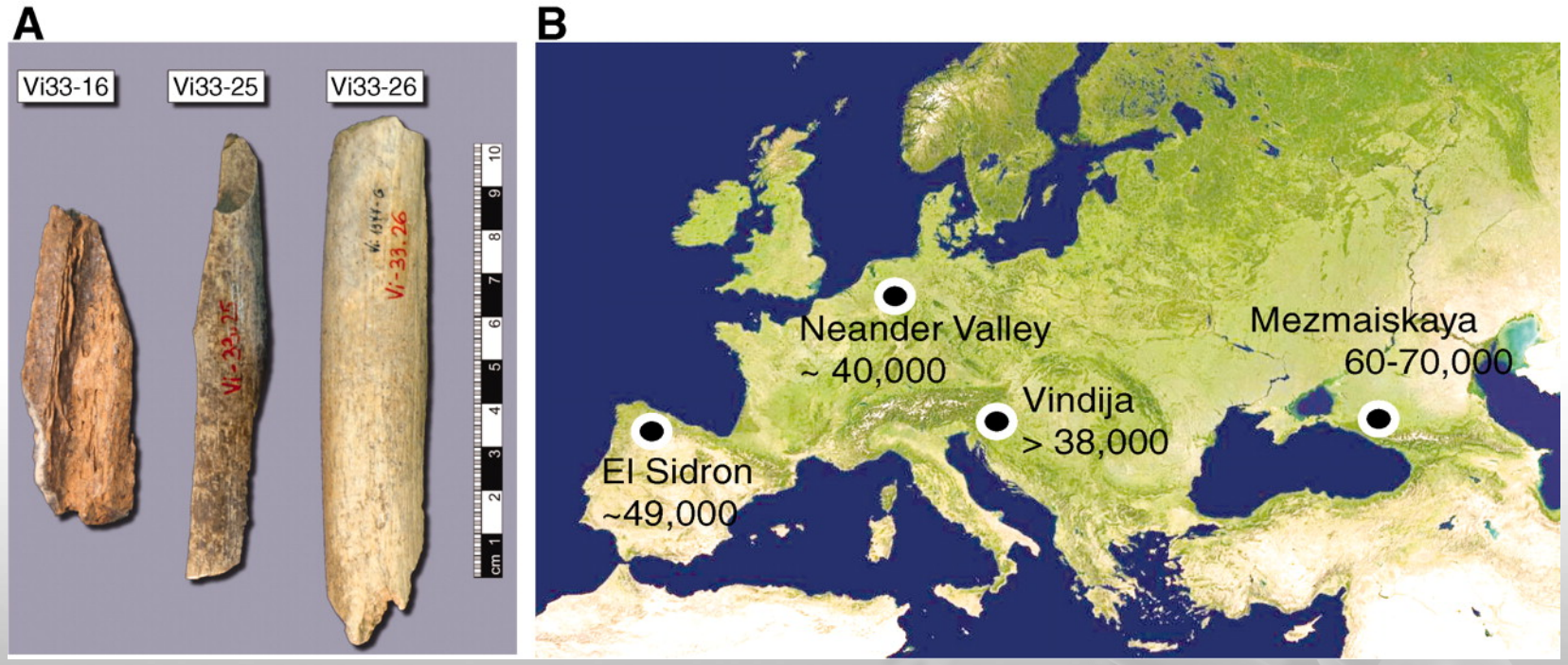
Interdisciplinary Collaboration to Improve Health Outcomes

# Genetic and Genomic Influences Across the Healthcare Continuum



# Example of DNA Stability
# Neanderthal Genome

**Fig. 1 Samples and sites from which DNA was retrieved.**




Richard E. Green et al. A Draft Sequence of the Neanderthal Genome. Science 2010;328:710-722

# Genetic/Genomic Information

- Genetic and/or genomic tests can be performed on stored biospecimens
  - Tissue blocks
  - DNA banking
  - Prior specimen collections
  - Collections within 24 hours of death

# Considerations in the Genomic Era

- Who is the "patient"
  - Individual **AND** family **AND** community **AND** population
  - Can be healthy with only a predicted risk for a health condition or suffering from a health condition
  - Extend across the lifespan
    - Fetus through end of life and beyond

# Research Ethical Considerations

- Stability of DNA
  - Storage and future use
- Broad sharing of samples/data
- Limited control of downstream use
- Limited right to withdraw
- Identifiability
- Incidental findings
  - Duty to re-contact
- Implications for family/community

Kalia SS, et al. (2016). Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genetics in Medicine, ePub
Wolf, S., et al. (2012). Managing incidental findings and research results in genomic research involving biobanks and archived data sets. Genetics in Medicine, 14, 361-384
Rodriguez, L.L., et al. (2013). Research ethics: The complexities of genomic identifiability. Science, 339, 275-6.

# Research Versus Clinical

| Research | Clinical |
|---|---|
| Obligations | |
| Production of generalizable knowledge | Delivery of optimal healthcare |
| Protect participants from harm | Responsible for optimizing healthcare |
| Preserving the integrity of the research process | Providing care directed to the best interests of the patient |
| Receipt of information | |
| Not obligated to return results, but IF return results must meet criteria of analytic and clinical validity | Respect for autonomy |
| IRB oversight | HIPPA compliance |

*Legally-a communication is considered medical practice if it takes place in the **context** of physician/patient relationship and include rendering clinical care.

Burke et al. (2014). Return of results: Ethical and legal distinctions between research and clinical care. AJMG, 166C, 105-111.

# Genomic Knowledge

| | NNWFS | HOD | NCEMNA | MINC |
|---|---|---|---|---|
| Rate their understanding of the genetics of common diseases as EXCELLENT or VERY GOOD | 14% (n=73/510) | NA | 15% (n=53/364) | 7% (n=340/5091) |
| Have heard or read about the Genomic Nursing Competencies | 33% (n=166/506) | NA | NA | 9% (n=476/5250) |
| CORRECTLY answered question about whether genomic risk (as indicated by Fm Hx) has clinical relevance for coronary heart disease | 99% (n=437/442) | 98% (n=216/220) | 98% (n=363/372) | 99% (n=5108/5138) |
| INCORRECTLY stated that diabetes and heart disease are caused by a single gene variant | 61% (n=268/442) | 62% (n=137/220) | 54% (n=105/193) | 73% (n=3742/5138) |

# Interprofessional Healthcare Provider Knowledge

Stanek et al. 10,303 US physicians

- 98% agreed that genetic variation may influence drug response
- 10% felt adequately informed about pharmacogenomic (PGx) testing
- 85% had no PGx education in medical school
- 77% had no PGx in post grad training
- 29% had received PGx education

Stanek, EJ et al. (2012). Adoption of pharmacogenomic testing by US physicians: results of a nationwide survey. CPT, 91, 450-8.

# Interprofessional Healthcare Provider Knowledge

Stanek et al. 10,303 US physicians

- MDs with prior PGx education were more likely to have ordered PGx tests (OR1.63, 95% CI 1.34–1.97, $P < 0.001$)
- MDs who felt well informed about the availability and applications of PGx were more likely more likely to order PGx testing (OR 1.92, 95% CI 1.51–2.45, $P < 0.001$)

Stanek, EJ et al. (2012). Adoption of pharmacogenomic testing by US physicians: Results of a nationwide survey. CPT, 91, 450-8.

# Genomic Attitudes

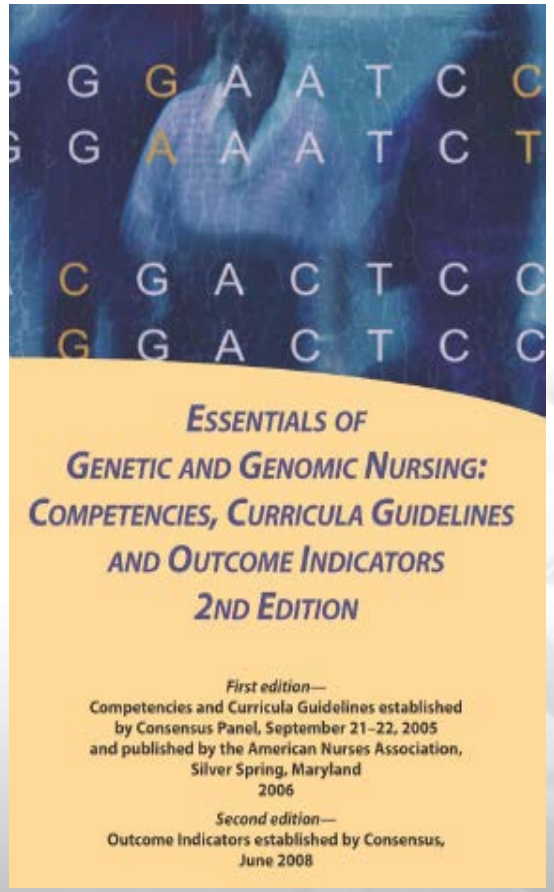
| | Reported it was SOMEWHAT OR VERY IMPORTANT for nurses to become more educated about genetics of common disease | Believe senior staff see genetics as an IMPORTANT part of the survey respondent's personal role | WOULD attend a genetics course on their own time |
|---|---|---|---|
| NNWFS | 92% (n=572/607) | Not assessed | 73% (n=368/506) |
| HOD | 98% (n=239/244) | Not assessed | 75% (n=182/240) |
| NCEMNA | 97% (n=372/383) | 24% (n=87/356) | Not Assessed |
| MINC | 90% (n=6309/7108) | 25% (n=1342/5314) | 63% (n=3353/5292) |

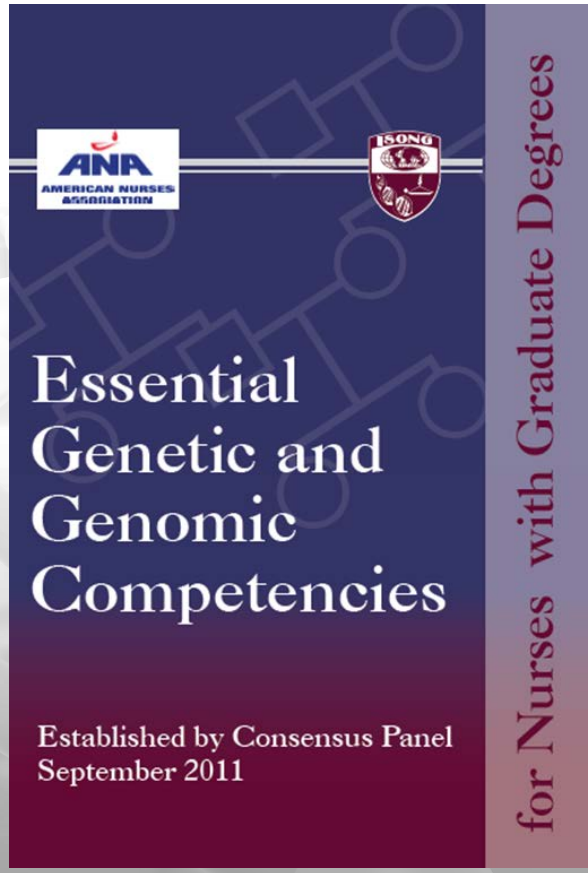
# MINC Genetic Education Impact

| | Prior Genetics Education | No Prior Genetics Education | P-value |
|---|---|---|---|
| Reported hearing or reading about the Competencies | 24.9% | 6.4% | <0.001 |
| Self described genetic/genomic knowledge and Good/Fair | 44.6% | 29.5% | <0.001 |
| Mean age of nurses reporting genetics in their curriculum | 41.8 years | 46.1 years | <0.001 |

# Essentials of Genetic and Genomic Nursing

- Define essential genetic and genomic competencies for **ALL** nurses regardless of level of academic preparation, practice setting or specialty
- Leveled for nurses with graduate degrees
- Both established by a process of consensus



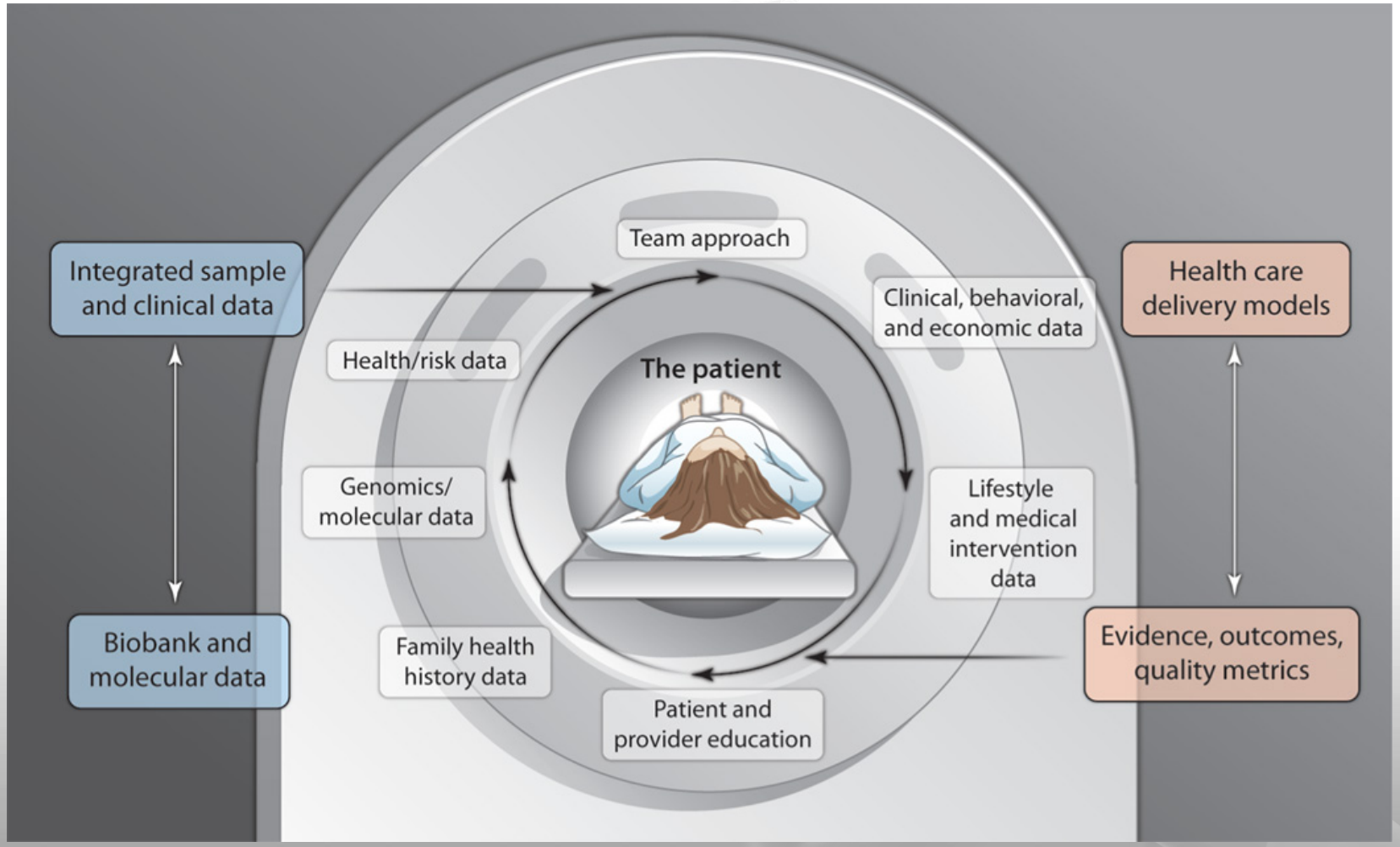




http://www.genome.gov/Pages/Careers/HealthProfessionalEducation/geneticscompetency.pdf
http://nursingworld.org/MainMenuCategories/EthicsStandards/Genetics-1/Essential-Genetic-and-Genomic-Competencies-for-Nurses-With-Graduate-Degrees.pdf

# The Quest for Personalized Health Care

- Use of an individual's genetic/genomic information In addition to traditional health information to guide health care decision-making
- Disease prevention, risk reduction, diagnosis, treatment, symptom management and palliative care
  - Pharmacogenomics
    - Medication selection
    - Dose selection
    - Inhibitors
    - Inducers

# Personalized Health Care Requirements




Ginsburg G S et al. Sci Transl Med 2011;3:101cm27-101cm27

Science Translational Medicine
AAAS

# Genomics is a Complex Competency

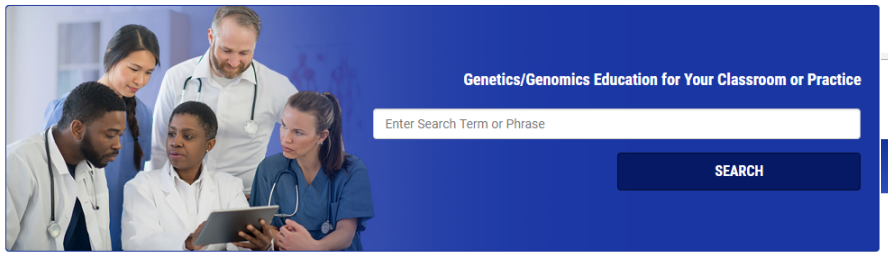
- Little to no foundational underpinning in genomics
  - Differs from other change initiatives i.e. end of life
- Outcomes of appropriately used genomics applications may not be observable
  - Lack of observability slows adoption rates
- The language of genomics is not understood by the general healthcare provider
  - Limits capacity to read and understand the literature
- Genomic applications require infrastructure
  - i.e. point of care decision support, documentation capacity

# Genomics is a Complex Competency, cont

- Waiting for the future workforce to solve this problem is unrealistic
  - Evidence documents that faculty genomic knowledge is equivalent to the students
  - Existing board and certification exams have limited genomic content
- The existing training model that includes clinical experiences is not feasible in the absence of clinical integration
  - Novel strategies for training need to be considered
- This is an interprofessional competency issue
  - You may not have a colleague to go to for help

Read, C. et al. (2017). Misconceptions About Genomics Among Nursing Faculty and Students. Nursing Education, Epub ahead of print.

# Genetics/Genomics Competency Center




GENETICS / GENOMICS COMPETENCY CENTER

Home | About | Competencies | Browse Topics

**What is G2C2?**

- Online repository of genomics educational materials
- Peer-reviewed collections for genetic counselors, nurses, pharmacists, physician assistants, and physicians
- Professional editorial board curates every resource
- Resources are mapped to discipline-specific genomic competencies

**How to use G2C2?**

- Search for resources using terms, topics, disciplines, or genomic competencies: Examples **for Genetic Counselor Educators** and **Nurse Educators**
- Search for genomics educational resources sponsored by professional societies
- Save resources for easy retrieval
- Submit resources for consideration

Home | About | Competencies | Browse Topics

## Competencies

| Nurse | Physician Assistant | Pharmacist | Genetic Counselor | Physician |
|---|---|---|---|---|
| COMPETENCIES MAP | COMPETENCIES MAP | COMPETENCIES MAP | COMPETENCIES MAP | COMPETENCIES MAP |
| Print Version | Print Version | Print Version | Print Version | Print Version |
| **Reference** | **Reference** | **Reference** | **Reference** | **Reference** |
| Essentials of Genetic & Genomic Nursing: Competencies, Curricula Guidelines, & Outcome Indicators, 2nd Edition (2008) | Physician Assistant Genomic Competencies (2016) | Pharmacogenomics Competencies in Pharmacy Practice: A Blueprint for Change (2016) | Practice-Based Competencies for Genetic Counselors (2014) | Framework for Development of Physician Competencies in Genomic Medicine (2014) |

GENETICS / GENOMICS COMPETENCY CENTER

Home | About | Competencies | Browse Topics

## Search Results

**Filter Options**

Click on the selections below to narrow your search further

Clear All

**Disciplines**

- Genetic Counselor (22)
- Nurse (27)
- Pharmacist (57)
- Physician (22)
- Physician Assistant (32)

**CME/CE Availability**

- All
- Yes (11)
- No (84)

**Cost**

- All
- Paid (20)
- Free (75)

**Formats**

- Article (12)
- Book (16)
- Course (13)
- Guideline (30)
- Other (16)
- Website (46)

You searched for: pharmacogenomics Search Again

There are **95** results that match your search.

Display 10 results per page « 1 2 3 4 5 »

| Resource Title | Type | CME | Cost |
|---|---|---|---|
| American Association of Colleges of Nursing Webinar Series: Genomics | Multimedia | No | Free |
| ClinGen | Website | No | Free |
| Clinical Pharmacogenetics Implementation Consortium (CPIC) | Website | No | Free |
| HLA-B alleles and adverse events related to use of carbamazepine and allopurinol | Other | No | Free |
| International Society of Nurses in Genetics (ISONG) | Society/Organization | - | - |
| ISONG Webinar: Pharmacogenetics and Your Clinical Practice | Website | No | Paid |
| NSGC Webinar: Pharmacogenetics: Practical Information for Genetic Counselors | Other | No | Free |
| Personalized Medicine Coalition | Website | No | Free |
| Pharmacogenomics Education Program (PharmGenEd) | Website | No | Free |
| RxGenomix Training Program in Pharmacogenomics | Course | Yes | Paid |

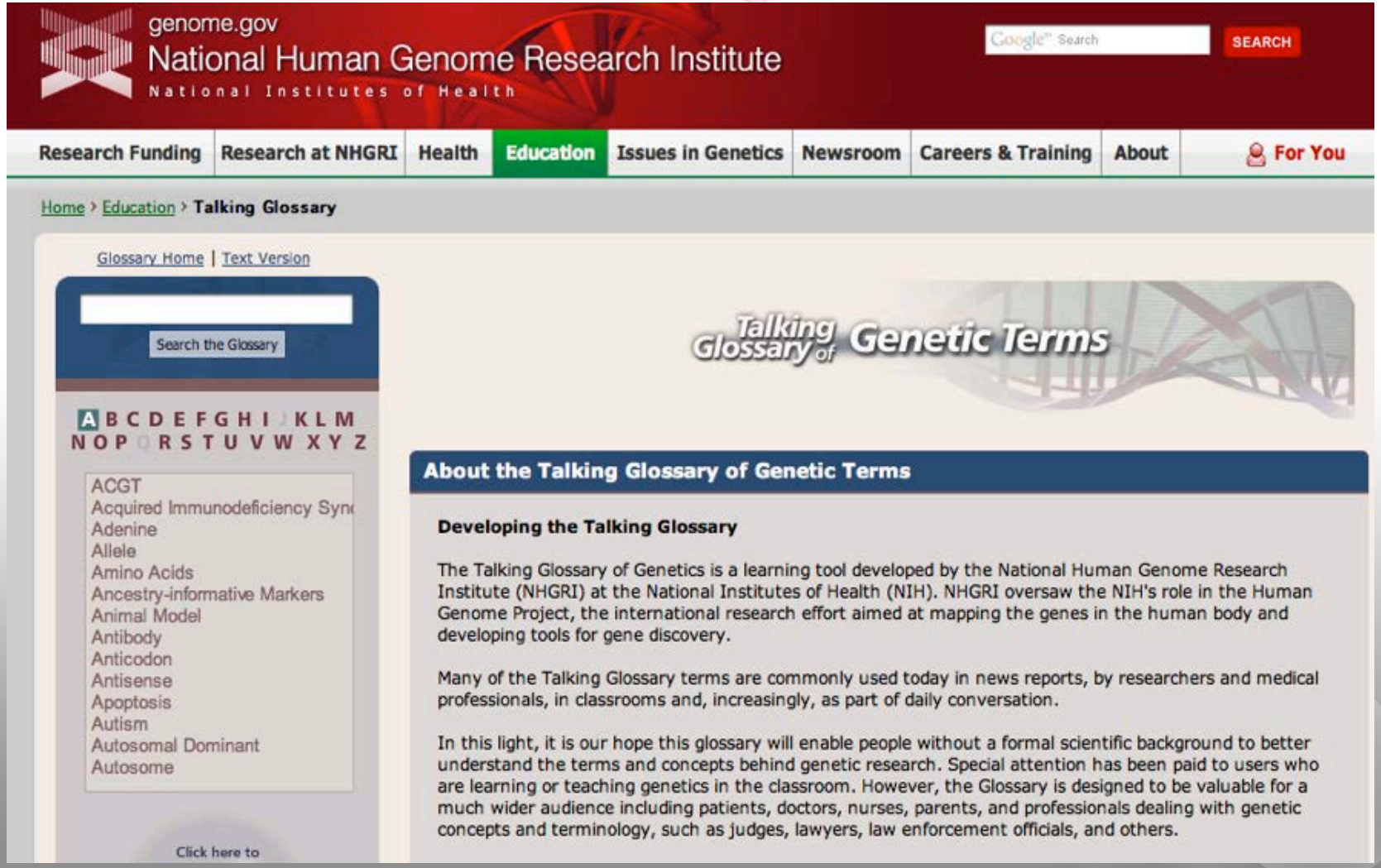
**https://genomicseducation.net/**

# Global Genetics and Genomics Community (G3C)

- High Fidelity Simulated Online Unfolding Case Studies
  - Ethnically diverse
  - Focus on common public health issues
- Portable, web-based, open access
- Interactive, self-paced, self-directed, unfolding case studies
- Utilizing professional actors as simulated patients
- Incorporates student/learner education activities and resources
- Faculty support includes suggestions on how to use cases in the curriculum

**http://genomicscases.net/en**

# Talking Glossary
# http://www.genome.gov/Glossary



GLOSSARY ON OFF

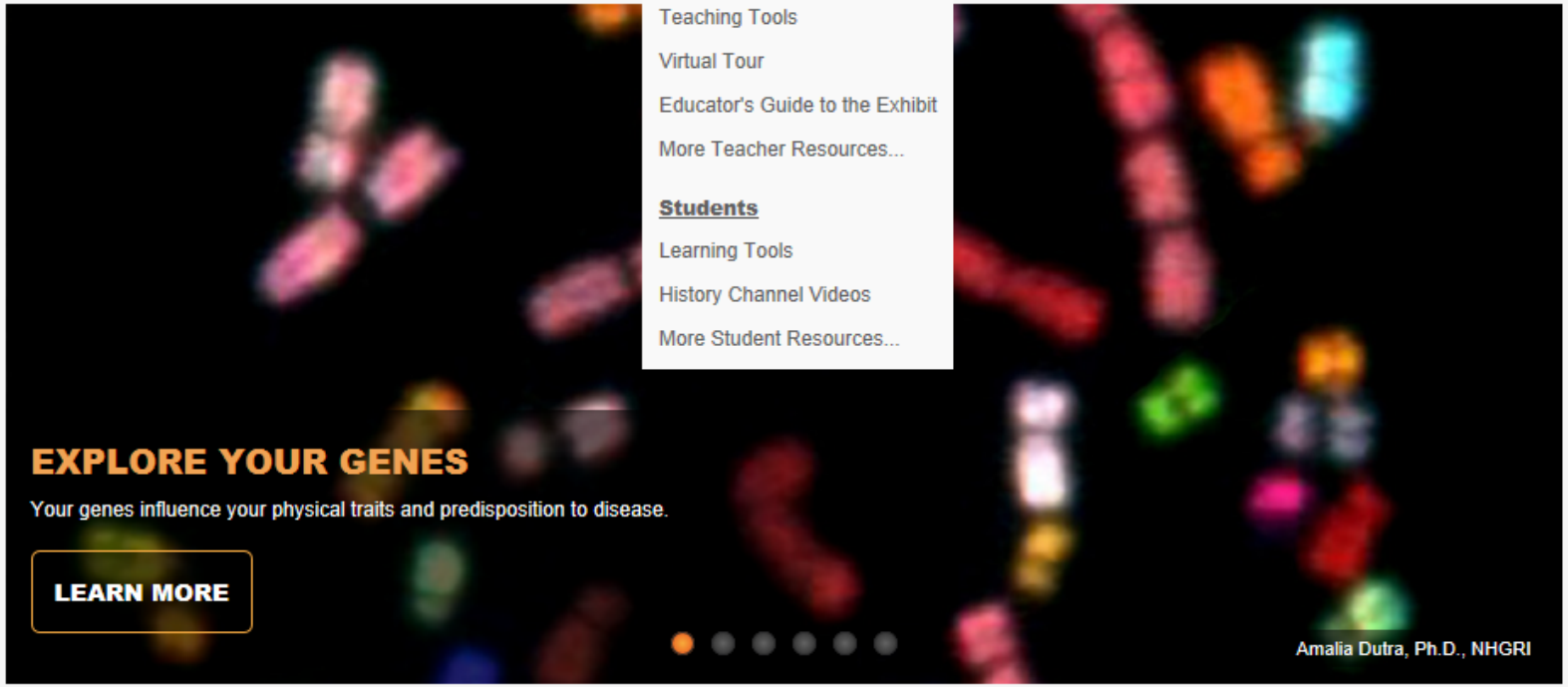
GENOME UNLOCKING LIFE'S CODE

EXPLORE | ABOUT | LEARN | TRAVELING EXHIBIT | MEDIA | CONNECTIONS

**Teachers**
- Curriculum
- Pinterest
- Teaching Tools
- Virtual Tour
- Educator's Guide to the Exhibit
- More Teacher Resources...

**Students**
- Learning Tools
- History Channel Videos
- More Student Resources...

HOME | EXPLORE | GENOMIC MEDICINE




# Genomic Medicine

You live at the dawn of an era of discovering and understanding the genome's role in health and disease. Many medical breakthroughs have already been enabled by genomics: developing ways to combat genetic illness, understanding the microbiome, personalizing health care, and stopping deadly epidemics. Advances in DNA sequencing enable you to investigate your own genome – and scientists are eager to use this knowledge for better health care. Explore the advances in genomic medicine and how genomic information can contribute to your

- OVERVIEW
- EXPLORE GENOMIC MEDICINE
- EXPLORE YOUR GENES

http://unlockinglifescode.org/

# Summary

- Recognize the relevancy and value of genomics to your role
- Evaluate your personal genomic competency and fill your competency gaps
- Utilize your leadership and skills to be a change agent/champion in your healthcare environment and within your professional organizations
- Recognize policy opportunities to ensure safe, effective and efficient translation of genomic clinical care
- Think creatively and be innovative about designing resources, education, infrastructures that facilitate appropriate adoption of genomics
- **National DNA Day-15th Anniversary-April 25, 2018**

https://www.genome.gov/dnaday/celebrate/

# Questions/Discussion

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240-760-6178