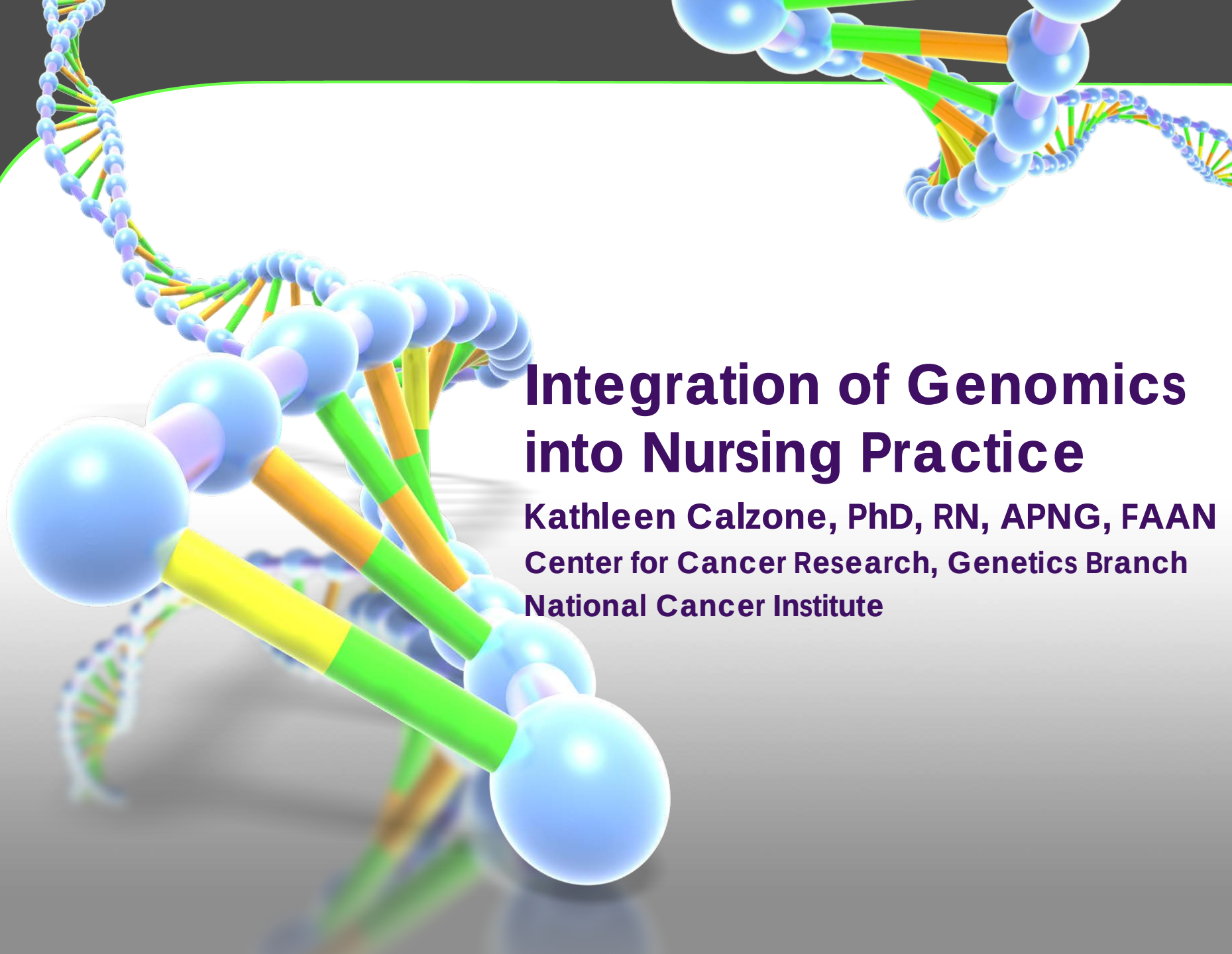
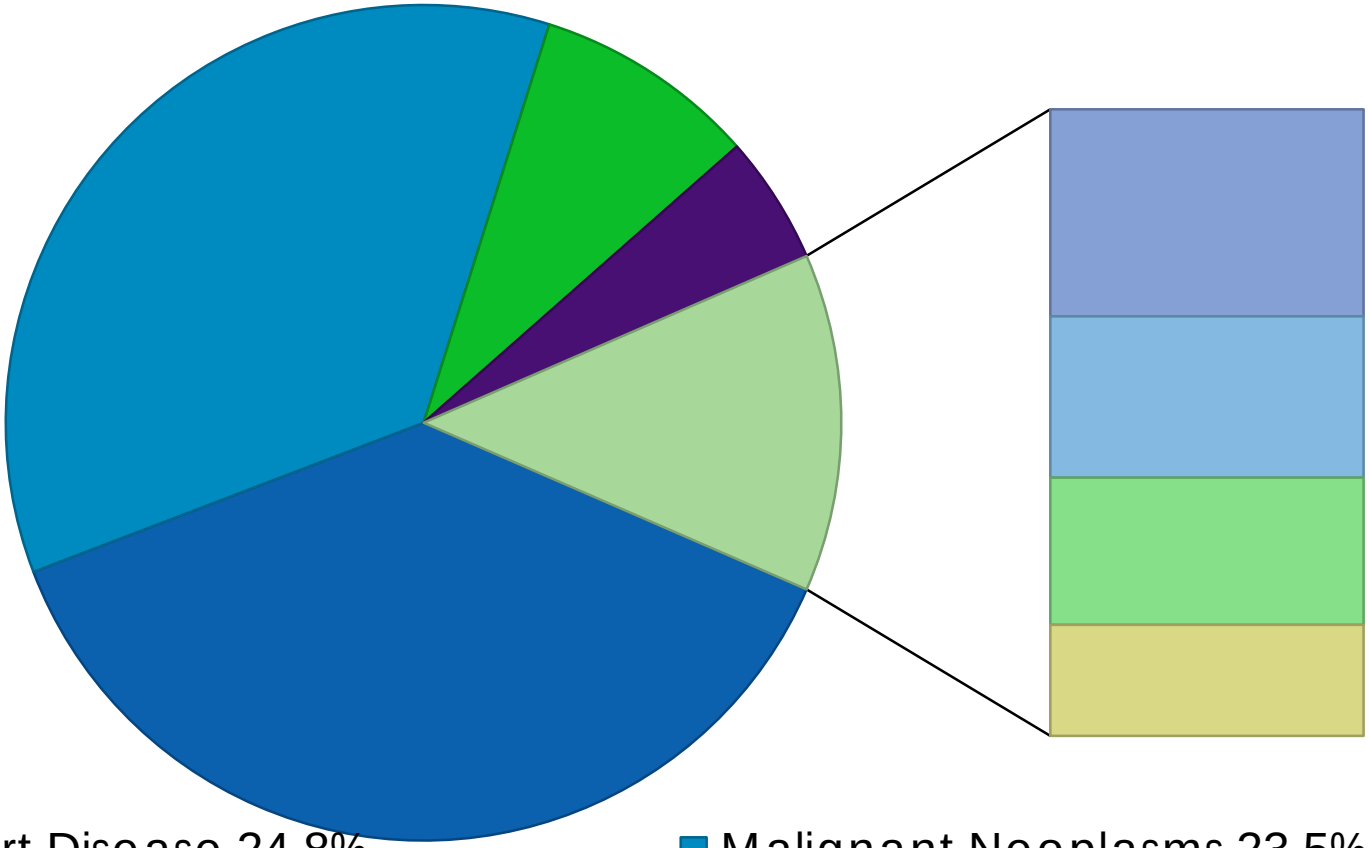


Integration of Genomics into Nursing Practice

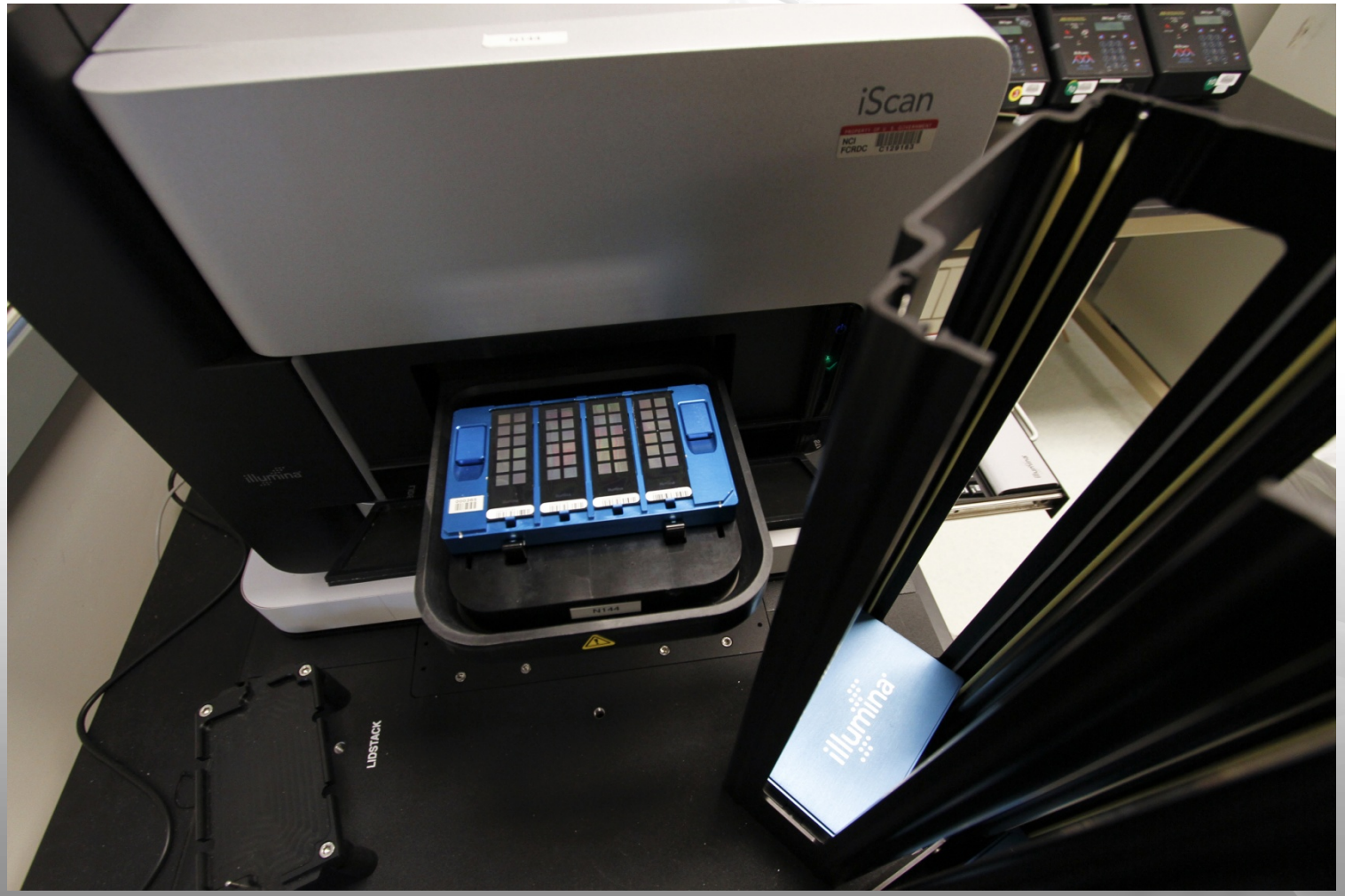
Kathleen Calzone, PhD, RN, APNG, FAAN
Center for Cancer Research, Genetics Branch
National Cancer Institute

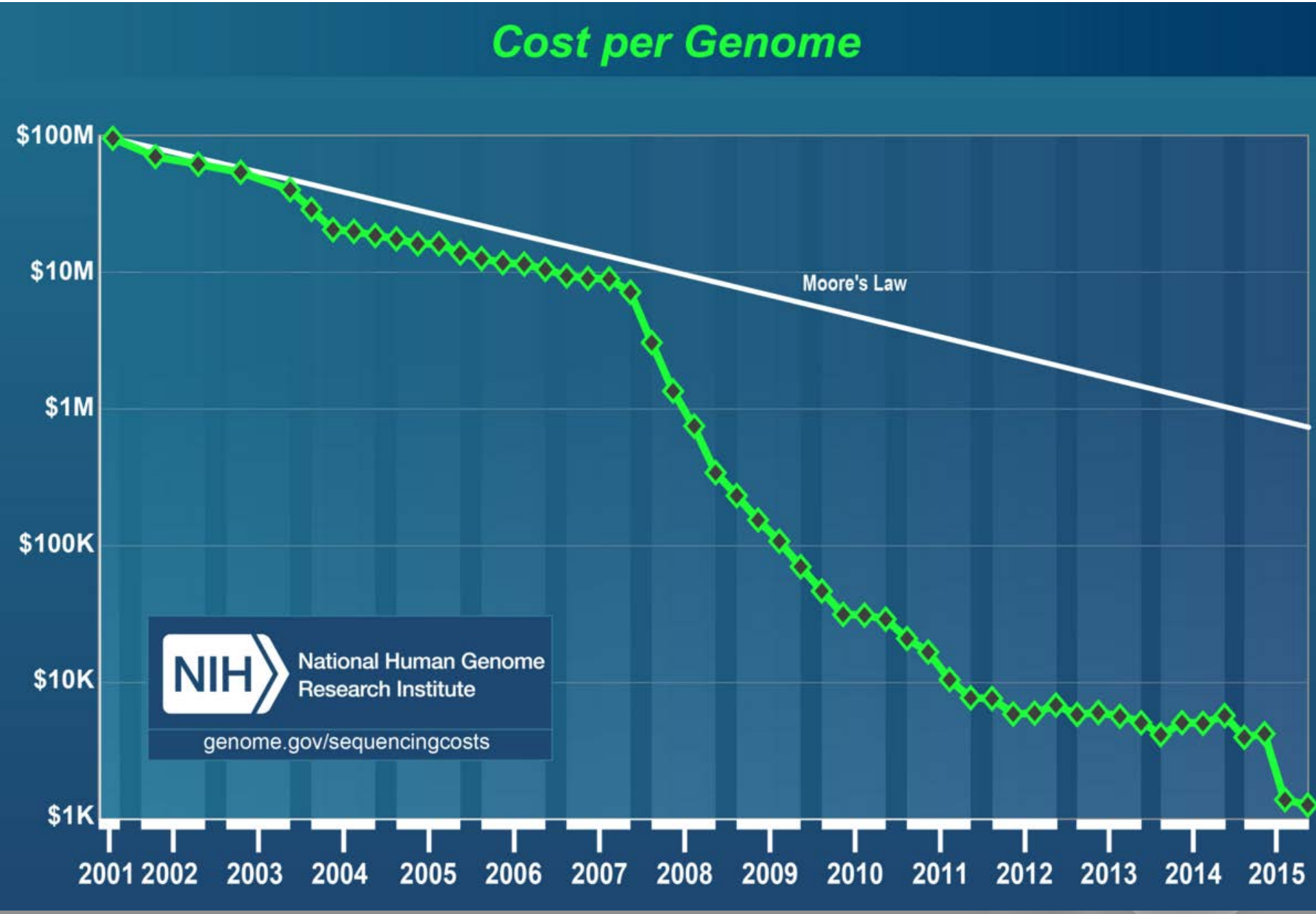
Top 10 Leading Causes of Death



- Heart Disease 24.8%
- Malignant Neoplasms 23.5%
- Chronic Respiratory Disease 5.7%
- Cerebrovascular 5.3%
- Unintentional Injury 4.8%
- Alzheimer's Disease 3.3%
- Diabetes Mellitus 2.9%
- Influenza & Pneumonia 2.2%
- Nephritis 2.0%
- Suicide

Emerging Science/Technology





http://www.genome.gov/27541954

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,

Precision Medicine

Precision Medicine

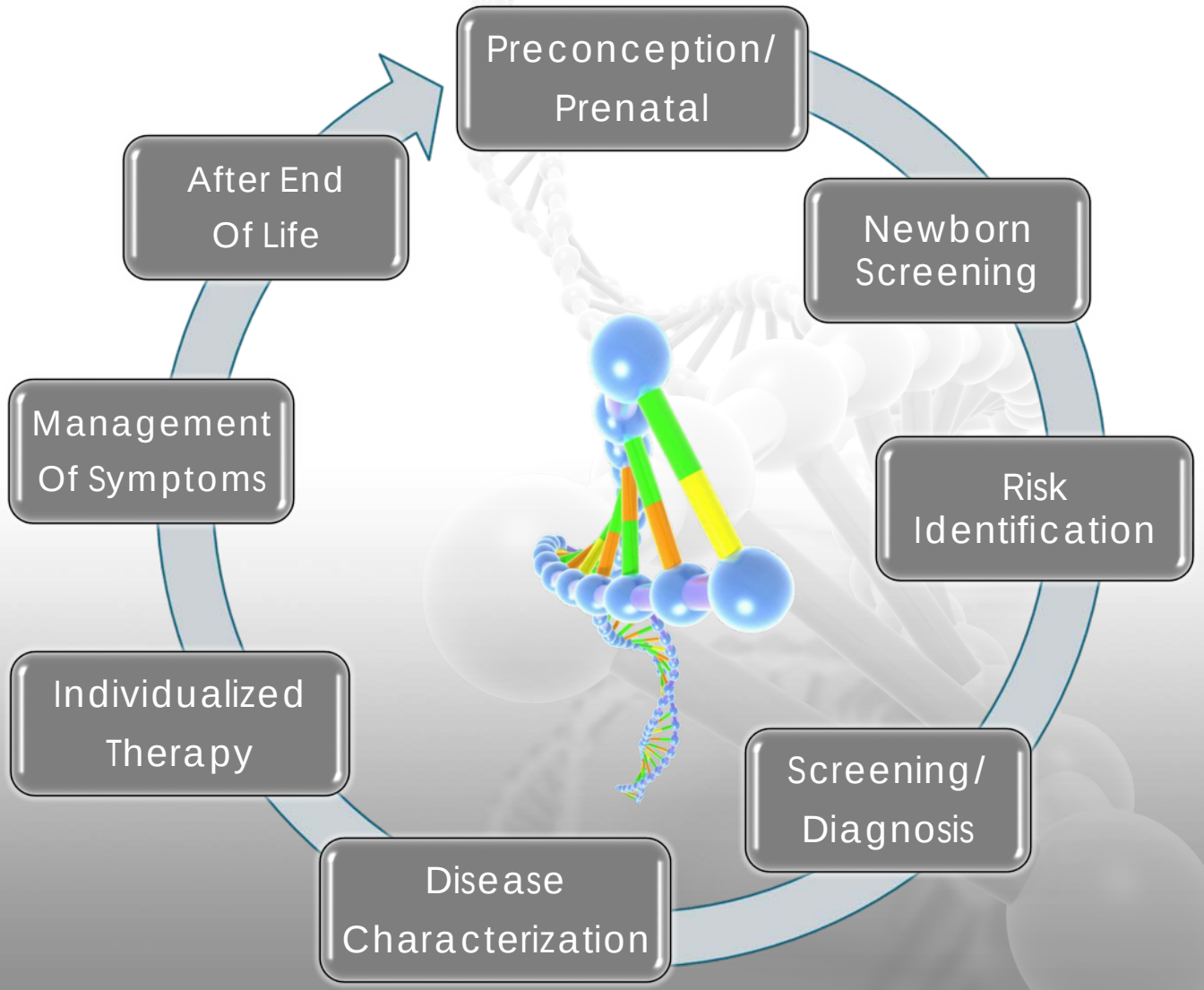
- Evolving taxonomy
  - Personalized Healthcare
  - Personalized Medicine
  - Precision Medicine
- Approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person

Precision Medicine Initiative

- Aim: Accelerate the pace of moving precision medicine into every day clinical practice
  - Expand research in cancer genomics
  - Establish a research cohort of >1,000,000 Americans
    - Share data, bio-samples, diet/lifestyle information, link to EHR if they choose
    - Who are Americans (i.e. citizens?)
    - Issues of diversity

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. (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

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.

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
- US Secretary of Health and Human Services Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (DACHDNC) provides national guidance about which health conditions should be included

Newborn Screening, cont

- Health conditions included in newborn screening panels vary by state
- States can opt to include screening for health conditions not recommended by the DACHDNC
- Health conditions recommended for screening meet the following criteria:
  - Adequate evidence that early diagnosis can improve health outcomes
  - Screening benefits outweigh possibility of harm

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.
- Newborn screening tests can provide false positive, false negative, or ambiguous results
- Newborn screening is conducted using a dried blood spot from a heel prick.
- Residual dried blood spots can be stored for future uses

Newborn Screening, cont

- 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
  - Funding for research exploring this type of technology application is being conducted
  - Plans for management of potential findings, changing evidence base of genetic variations identified and management of incidental findings

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

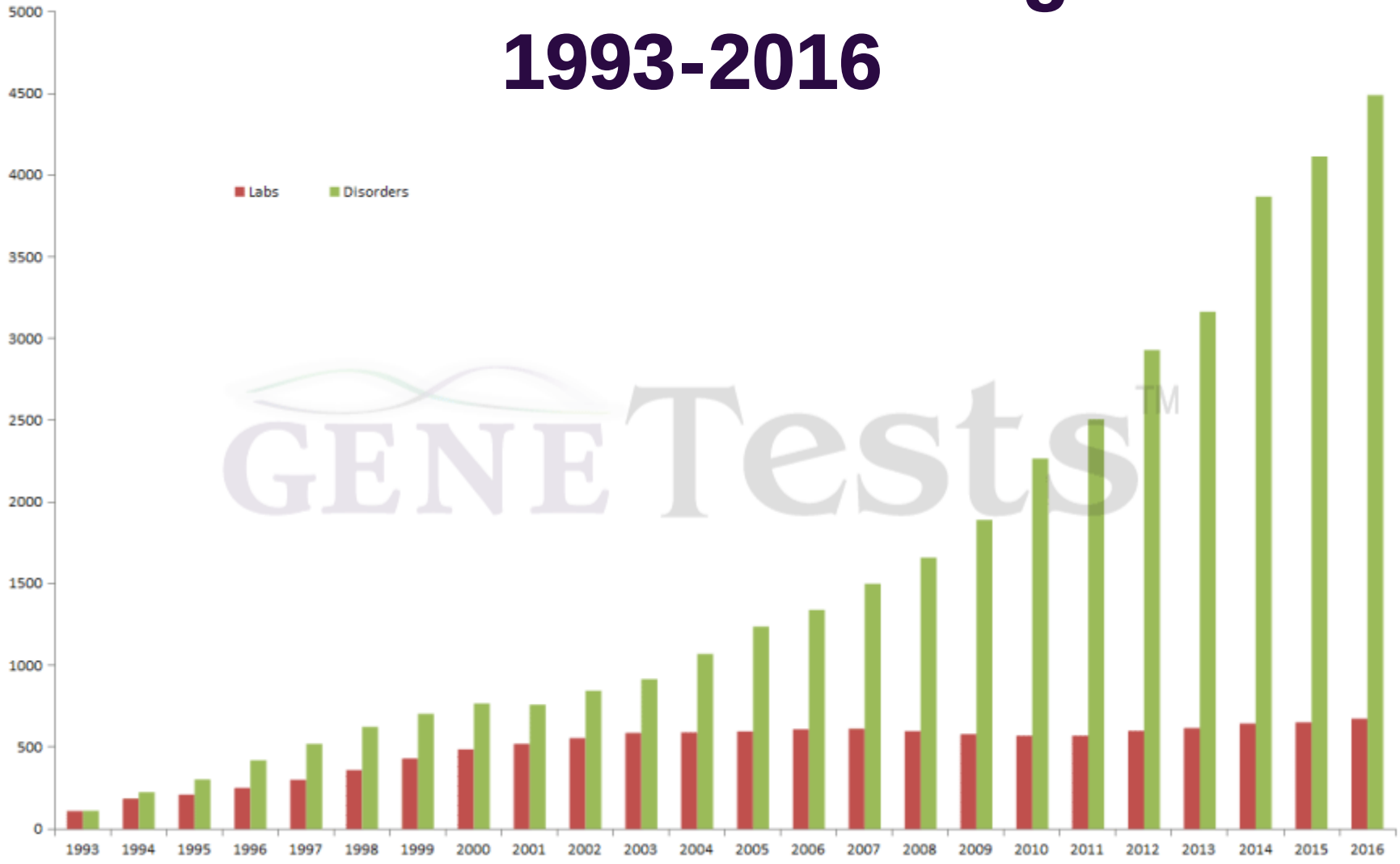
Family History

	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)

Disorders with Genetic Tests and Laboratories Offering Tests 1993-2016



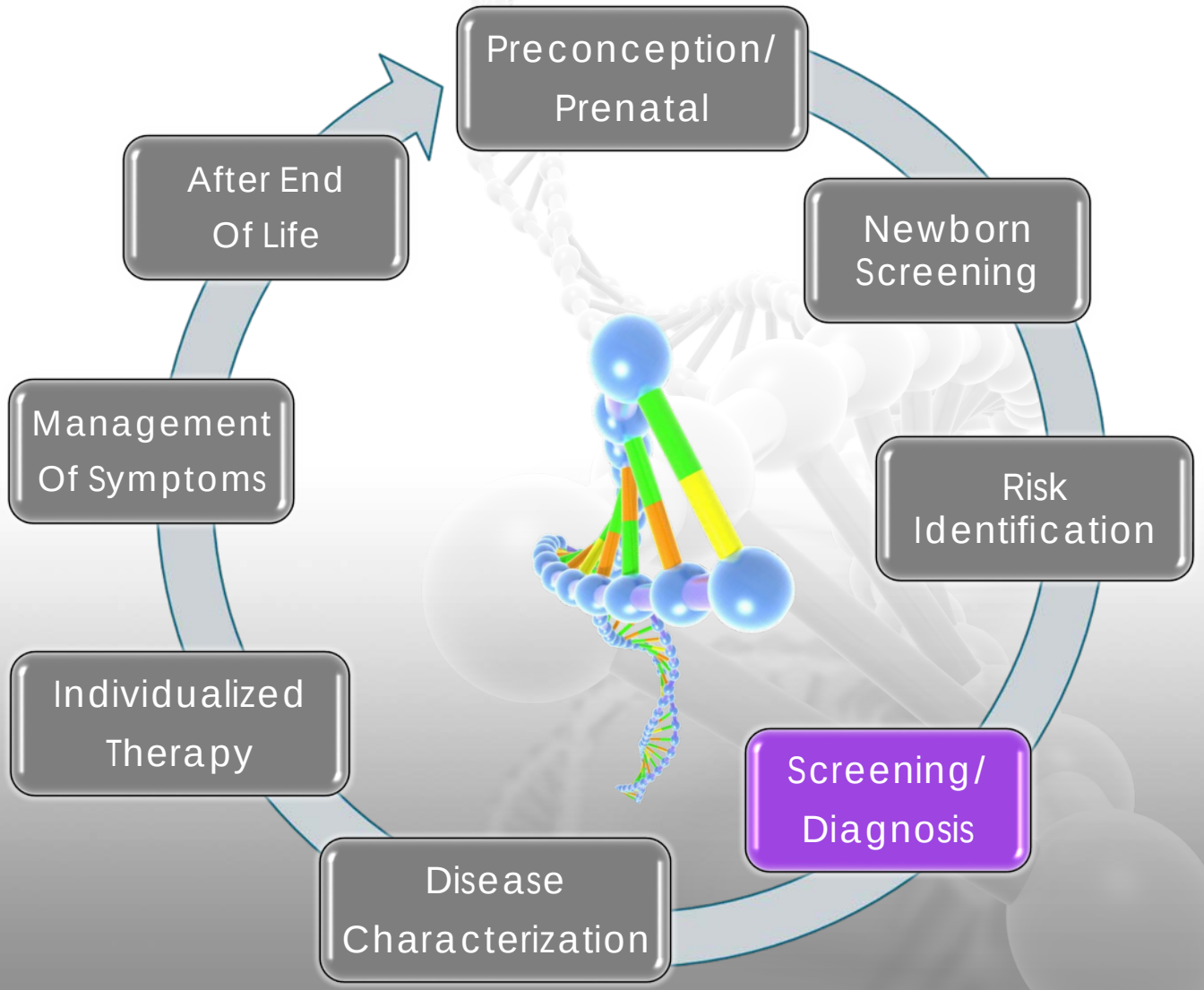
Family History in Nursing Practice

"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.

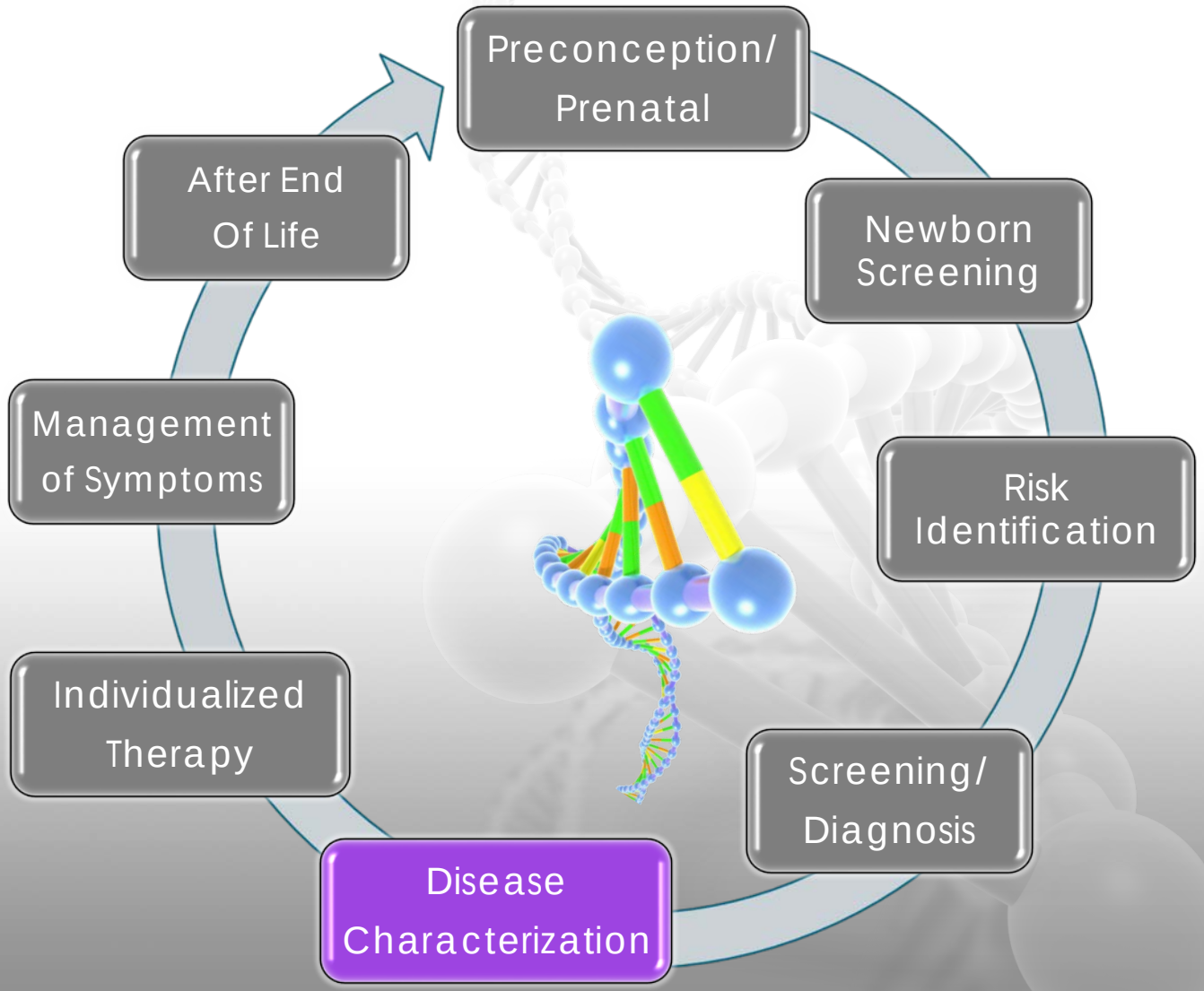
Screening

- 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

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

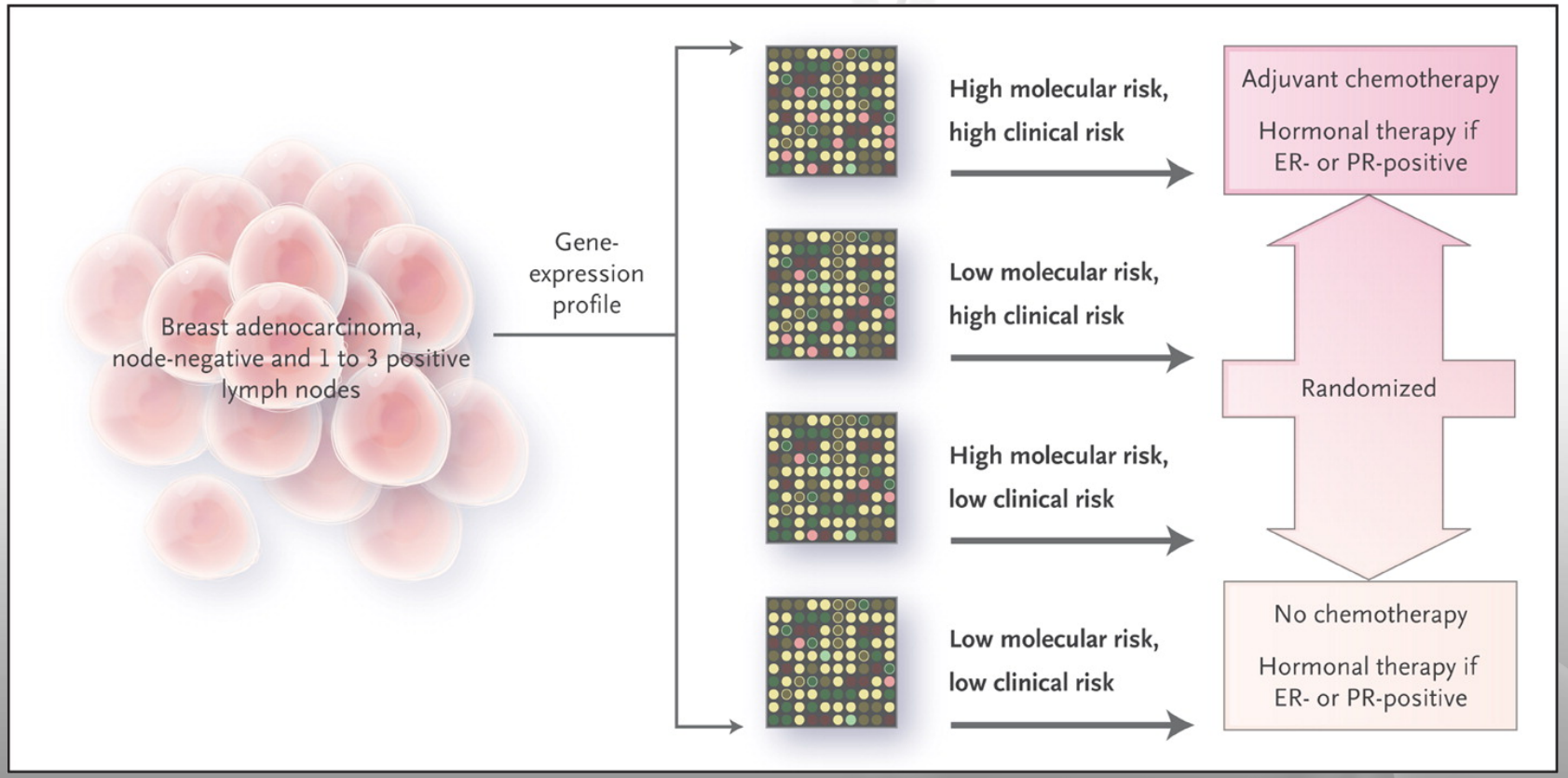
Interdisciplinary Collaboration to Improve Health Outcomes

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

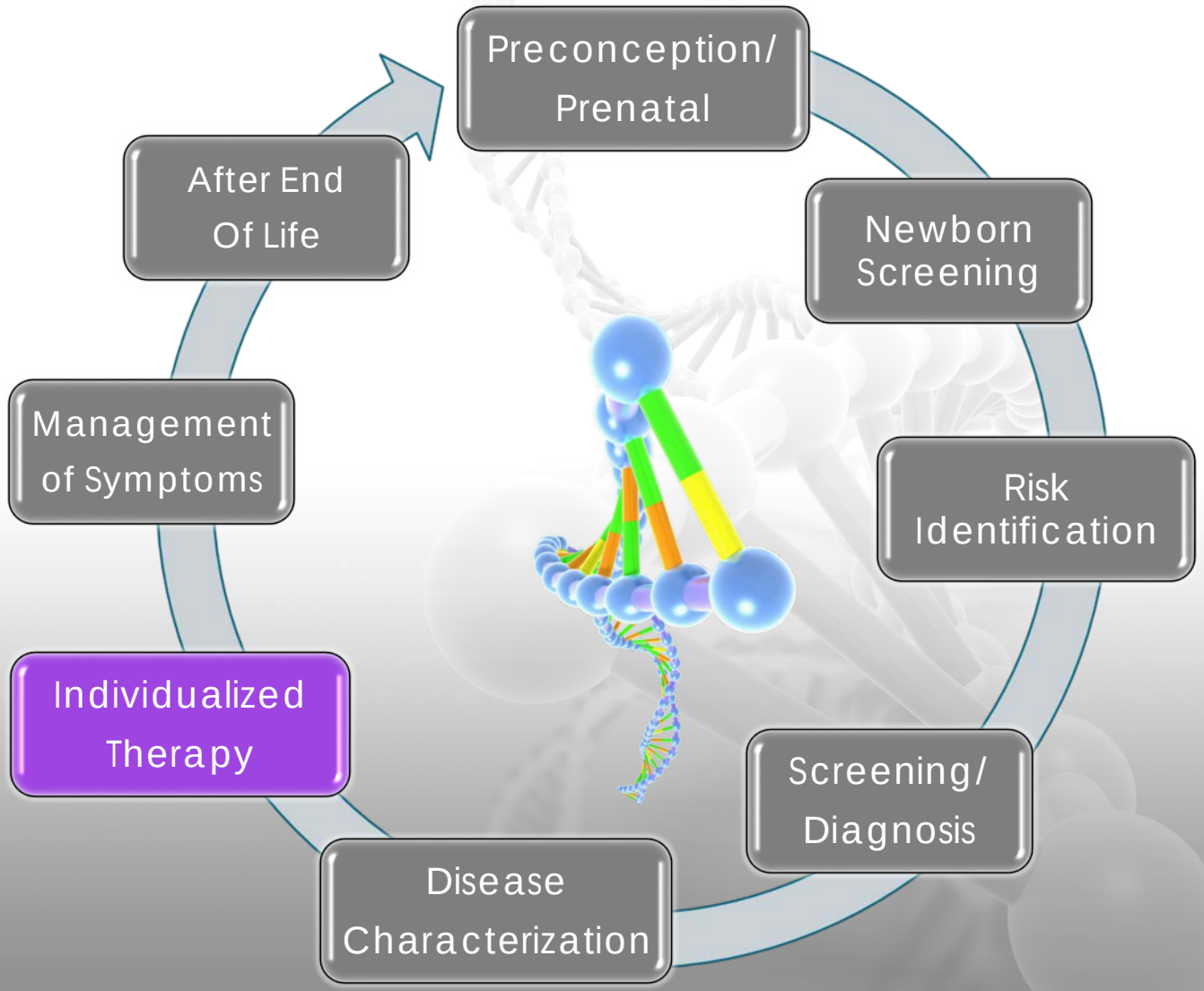


McDermott et al. (2011). Genomics and the continuum of cancer care, NEJM, 364, 350-360.

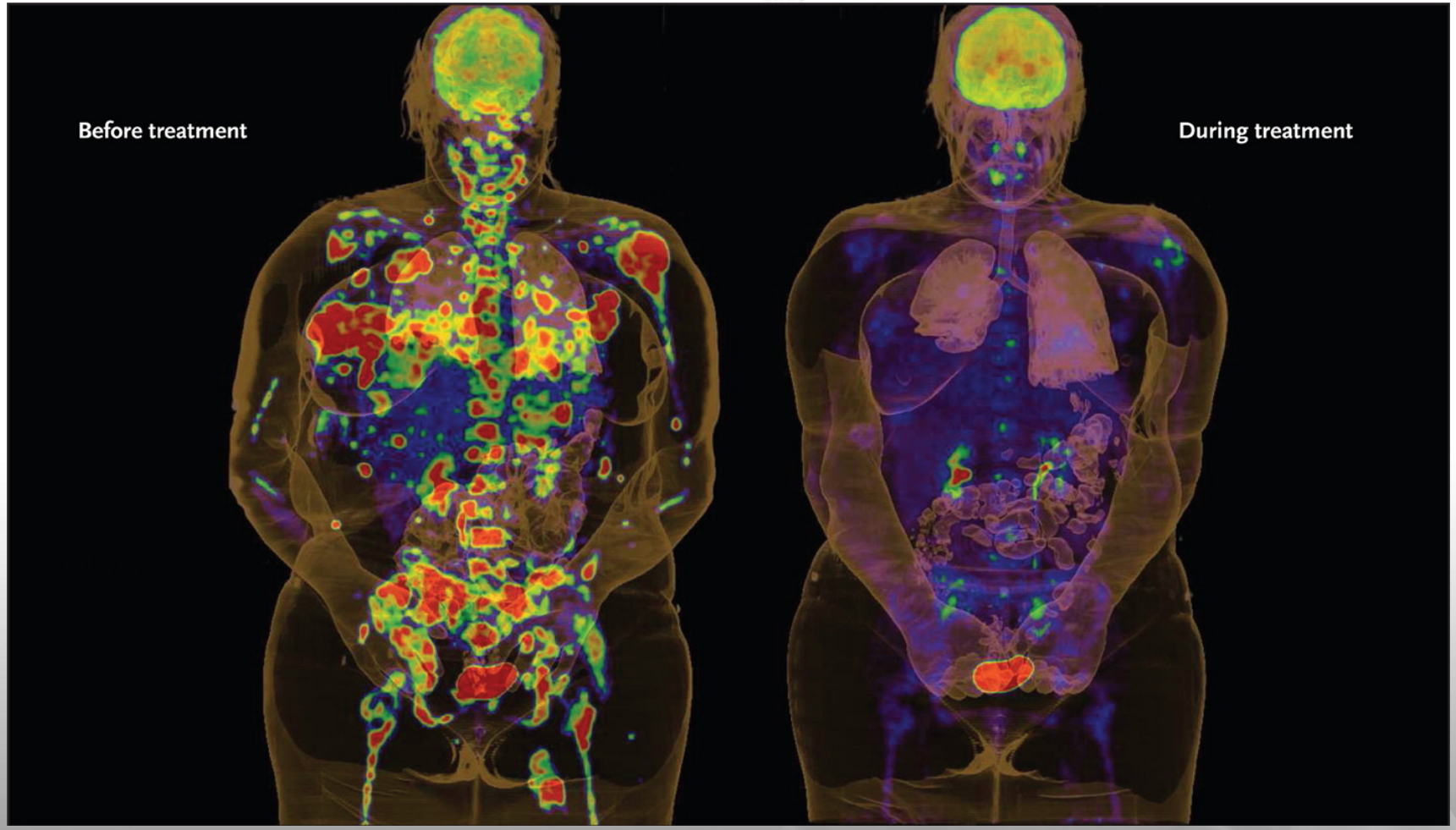
The NEW ENGLAND JOURNAL of MEDICINE

Interdisciplinary Collaboration to Improve Health Outcomes

Genetic and Genomic Influences Across the Healthcare Continuum



Targeting Treatment to a Specific Variant in the Melanoma Gene



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

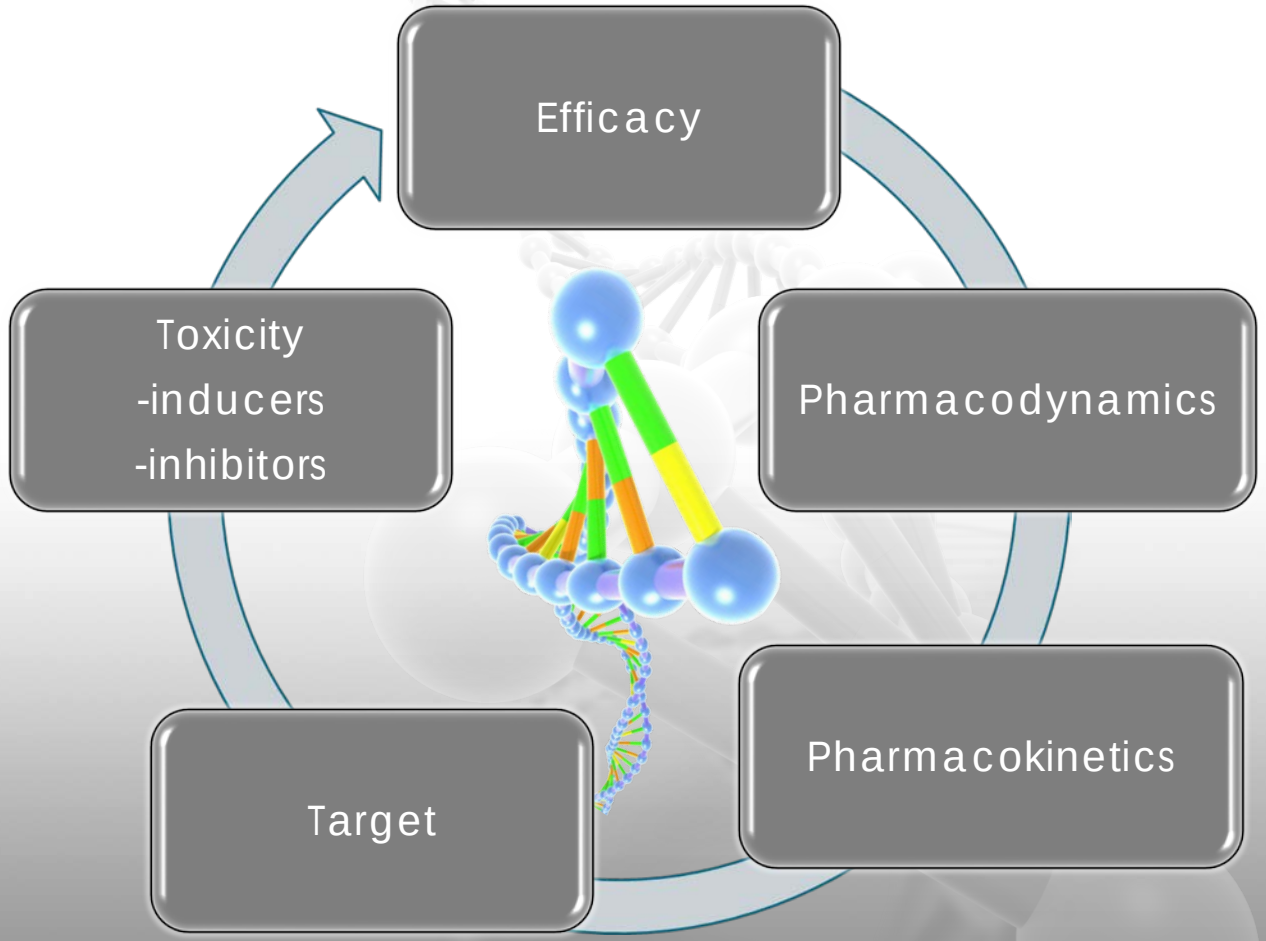
The NEW ENGLAND JOURNAL of MEDICINE

Cancer Tumor Profiling and Precision Medicine Trials

- Molecular Analysis for Therapy Choice (NCI-MATCH)
  - Identify mutations/amplifications/translocations in patient tumor sample and assign patient to relevant agent/regimen
- ClinOmics (NCI-Intramural)
  - Molecular, genomic, proteomic, metabolomics and other high throughput ("Omics") profiling on tumor and normal tissues for the identification of biomarkers and targets for therapy.
- Basket trials hypotheses
  - The presence of a molecular marker predicts response to a targeted therapy independent of tumor histology.

Redig A. et al. (2015). Basket trials and the evolution of clinical trial design in an era of genomic medicine. JCO, 33, 975-7.

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.

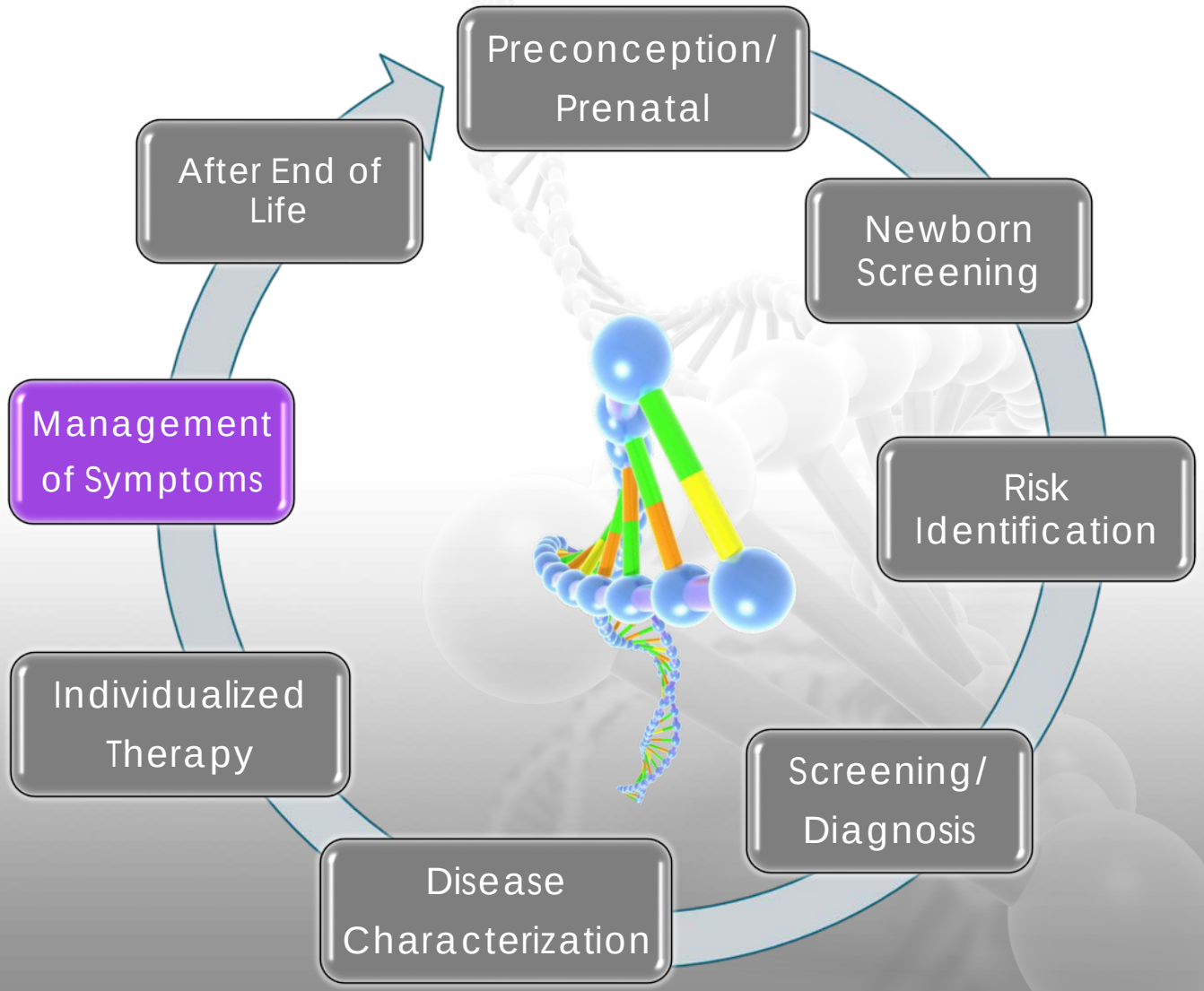
FDA Table of Pharmacogenomic Biomarkers in Drug Labeling

- 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
- 163 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

Interdisciplinary Collaboration to Improve Health Outcomes

Genetic and Genomic Influences Across the Healthcare Continuum



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

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.

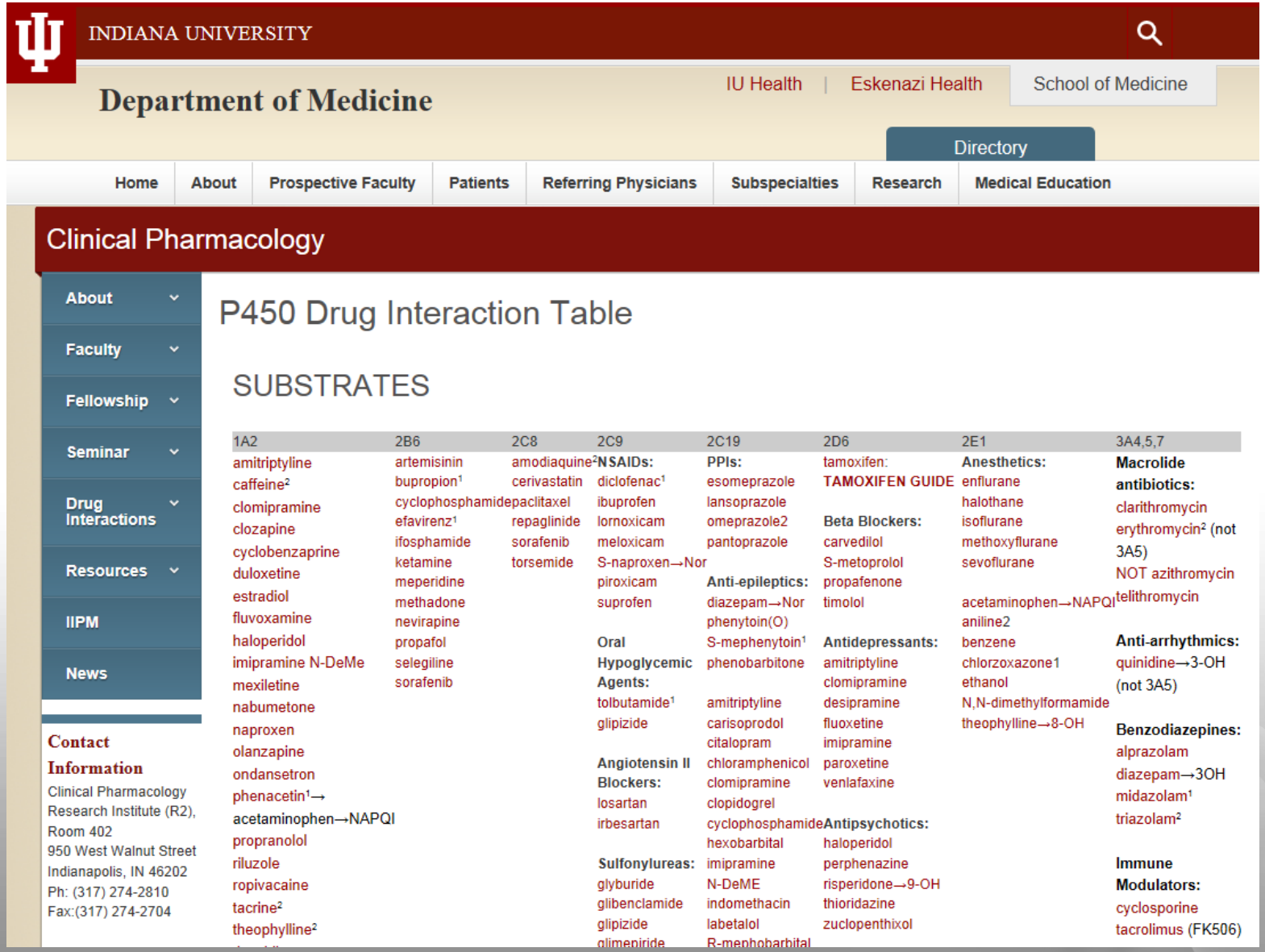
- A **Strong inhibitor** is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
- A **Moderate inhibitor** is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.
- A **Weak inhibitor** is one that causes a > 1.25-fold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

Indiana University Drug Interaction Table



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Clinical Pharmacology

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P450 Drug Interaction Table

SUBSTRATES

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
amitriptyline	artemisinin	amodiaquine[2]	**NSAIDs:**	**PPIs:**	tamoxifen:	**Anesthetics:**	**Macrolide antibiotics:**
caffeine[2]	bupropion[1]	cerivastatin	diclofenac[1]	esomeprazole	**TAMOXIFEN GUIDE**	enflurane	clarithromycin
clomipramine	cyclophosphamide	paclitaxel	ibuprofen	lansoprazole		halothane	erythromycin[2] (not 3A5)
clozapine	efavirenz[1]	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-mephenytoin[1]	**Antidepressants:**	benzene	**Benzodiazepines:**
mexiletine	selegiline		tolbutamide[1]	phenobarbitone	amitriptyline	chlorzoxazone1	alprazolam
nabumetone	sorafenib		glipizide		clomipramine	ethanol	diazepam→3OH
naproxen				amitriptyline	desipramine	N,N-dimethylformamide	midazolam[1]
olanzapine			**Angiotensin II Blockers:**	carisoprodol	fluoxetine	theophylline→8-OH	triazolam[2]
ondansetron			losartan	citalopram	imipramine		
phenacetin[1]→ acetaminophen→NAPQI			irbesartan	chloramphenicol	paroxetine		**Immune Modulators:**
propranolol				clomipramine	venlafaxine		cyclosporine
riluzole			**Sulfonylureas:**	clopidogrel			tacrolimus (FK506)
ropivacaine			glyburide	cyclophosphamide	**Antipsychotics:**		
tacrine[2]			glibenclamide	hexobarbital	haloperidol		
theophylline[2]			glipizide	imipramine	perphenazine		
			glimepiride	N-DeME	risperidone→9-OH		
				indomethacin	thioridazine		
				labetalol	zuclopenthixol		
				R-mephobarbital			

Contact Information

Clinical Pharmacology Research Institute (R2), Room 402
950 West Walnut Street
Indianapolis, IN 46202
Ph: (317) 274-2810
Fax:(317) 274-2704

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


NASCAR
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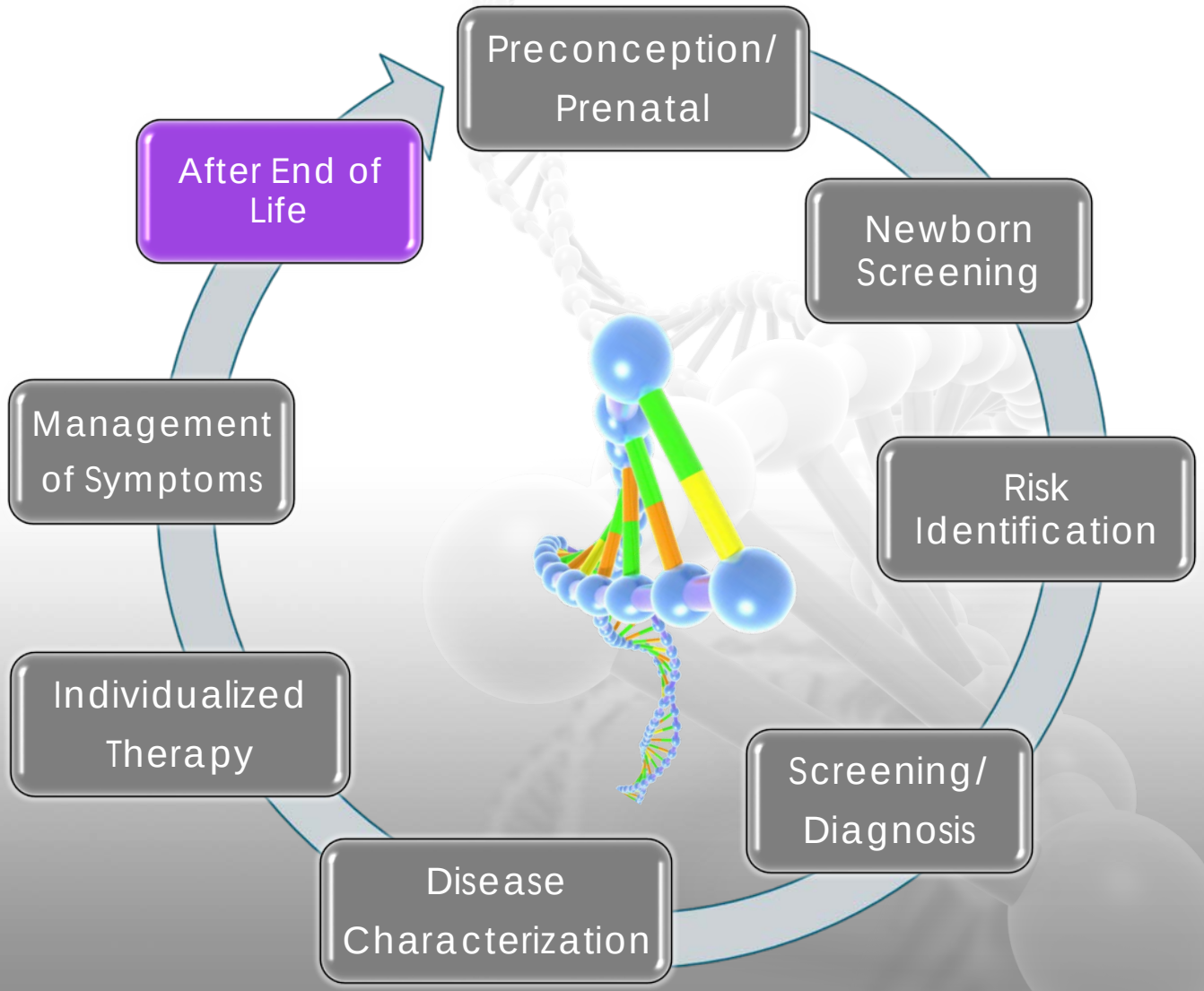
diet

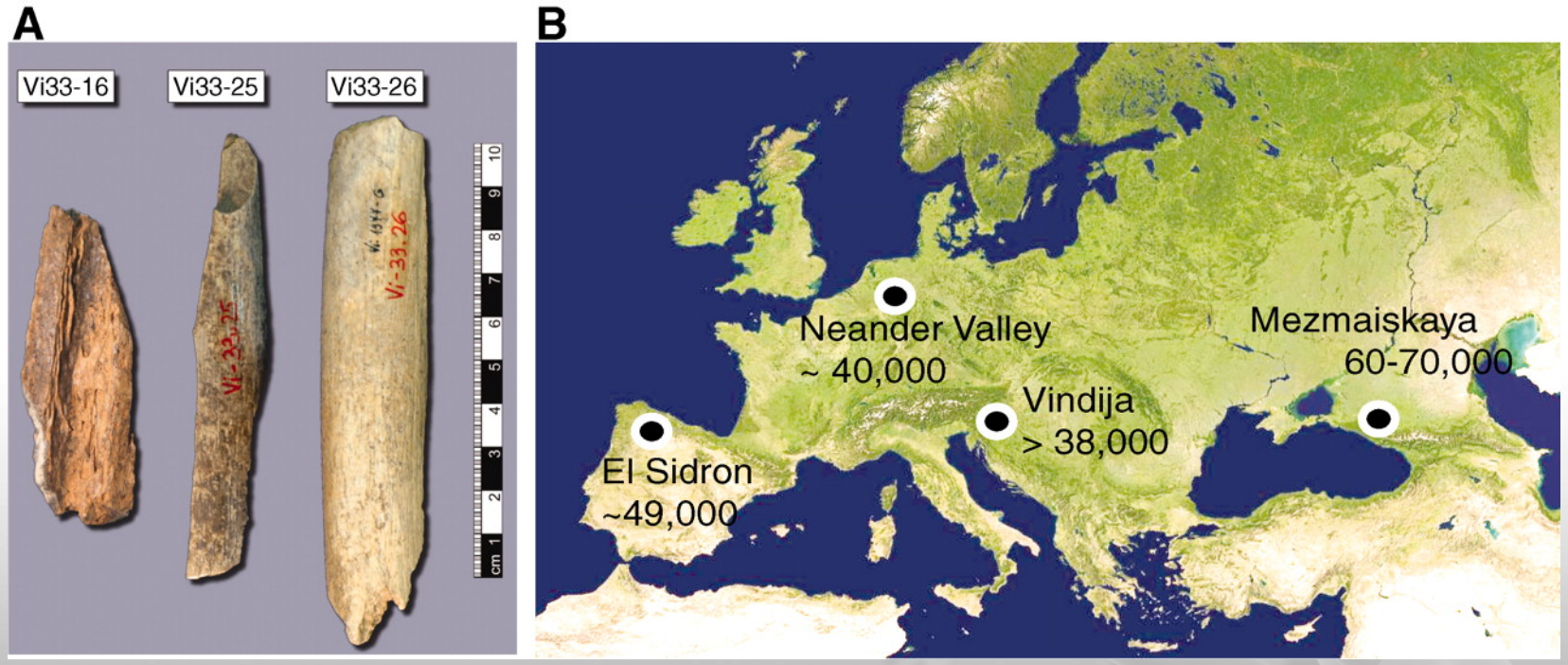
Interdisciplinary Collaboration to Improve Health Outcomes

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

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)

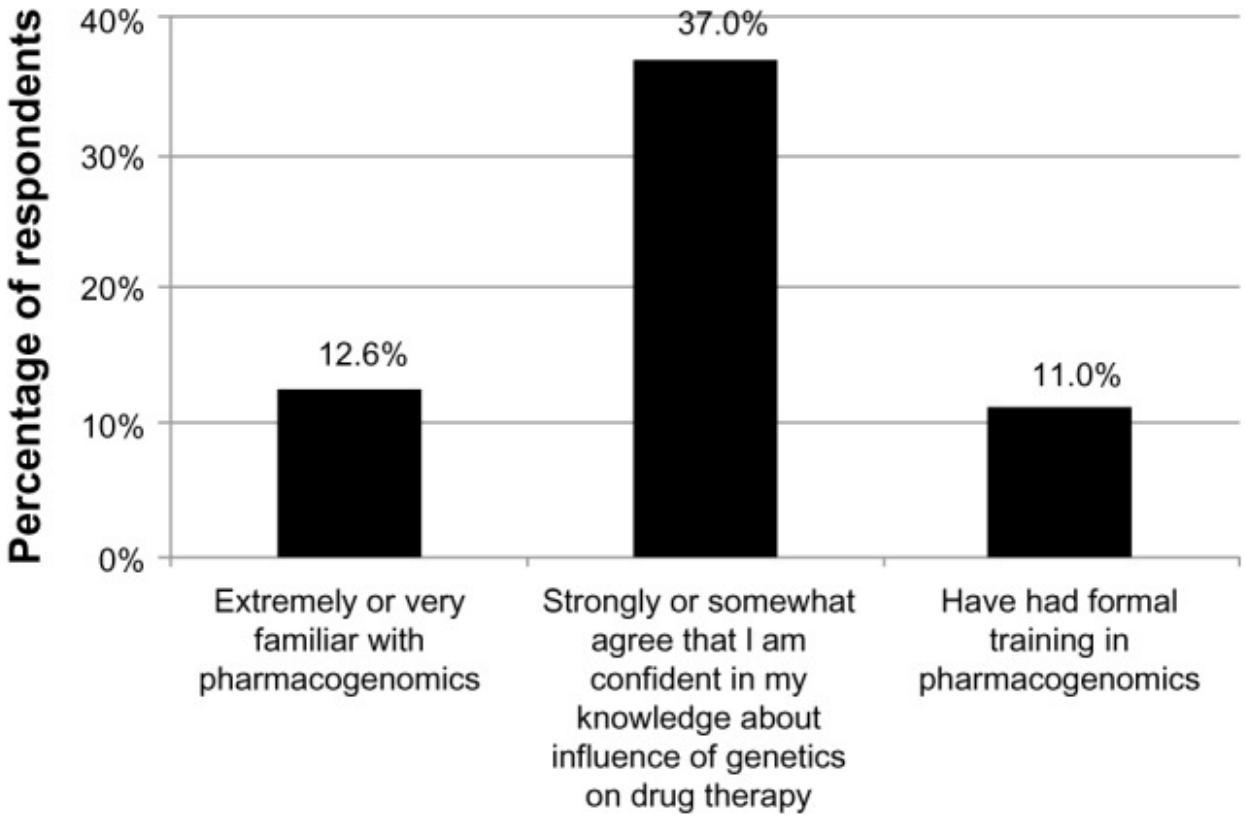
MINC Genetic Education Impact

	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

Pharmacogenomic Knowledge Gaps

AMA office based MD (n=300) survey

Figure 2

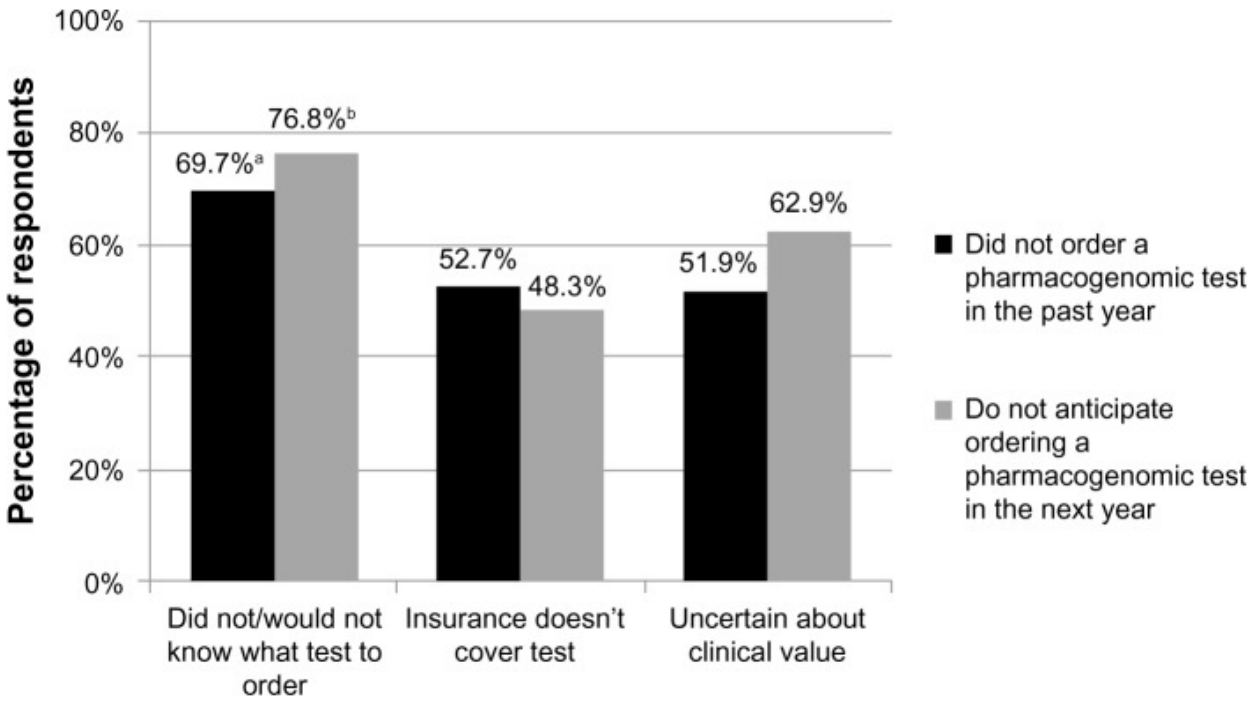


Familiarity with, confidence in and knowledge of, and training in pharmacogenomics, as reported by physician respondents. "Formal training" was defined as medical school, residency, or continuing medical education.

Taber et al. (2014). Pharmacogenomic knowledge gaps and educational resource needs among physicians in selected specialties. P&PM 7, 145-162.

Pharmacogenomic Knowledge Gaps

Figure 3



Reasons most commonly cited by physician respondents for not ordering a pharmacogenomic test in the past year, and for not anticipating ordering a pharmacogenomic test in the next year.

Notes: [a]Significantly more primary care physicians than cardiologists reported that they did not know what test to order (75.0% versus 52.5%, $P<0.05$); [b]significantly more primary care physicians and psychiatrists than cardiologists reported that they would not know what test to order (84.6% and 83.9%, respectively, versus 44.8%; $P<0.05$).

Taber et al. (2014). Pharmacogenomic knowledge gaps and educational resource needs among physicians in selected specialties. P&PM 7, 145-162.

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

Questions/Discussion

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