MEDINFO23

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Planning for Actionable Precision Medicine

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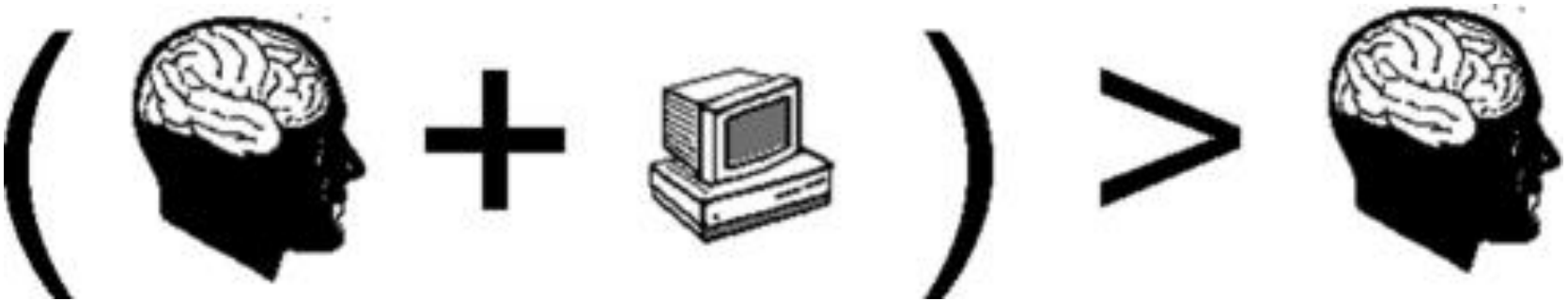
The Problem:

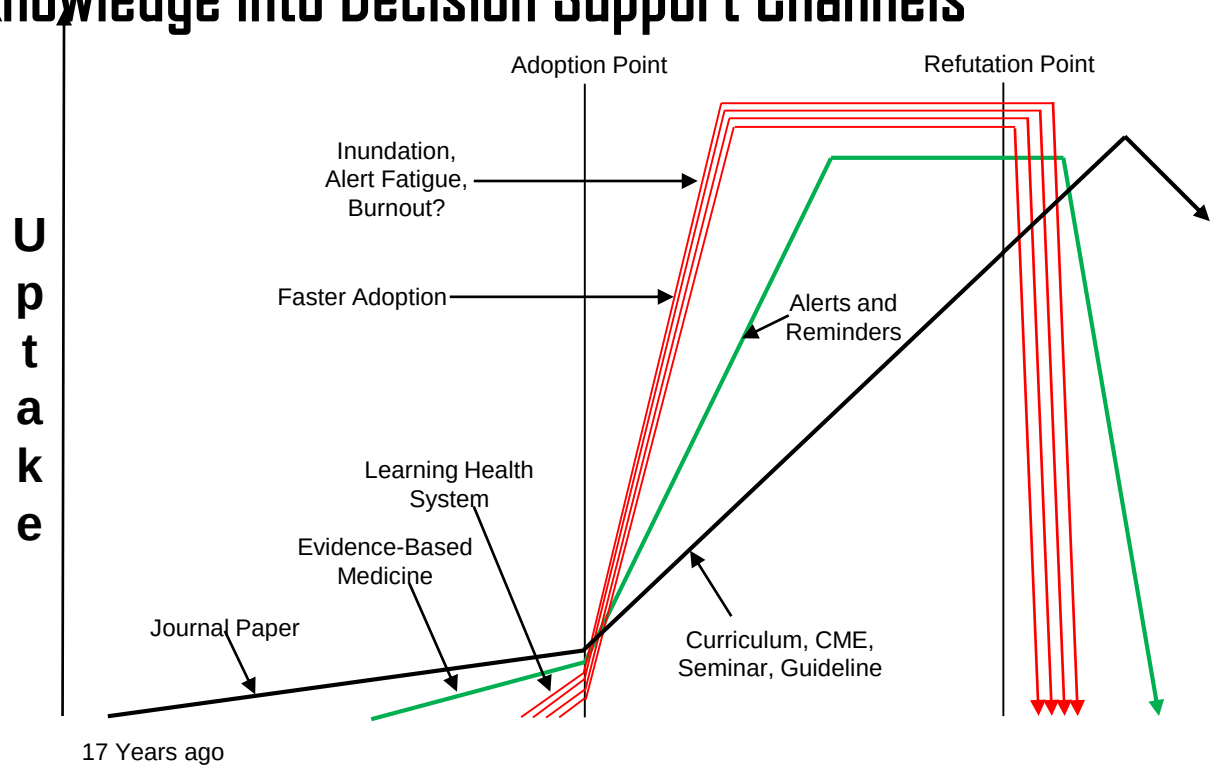
- Genomic-base recommendations are here now
- Patients' genomes will be in their records soon
- Machine learning will generate recommendations
  - Will accelerate without humans in the loop
  - Won't be explainable
  - Won't be learnable or memorizable
  - Will not be maintainable in "classic" decision support
  - Will worsen alert fatigue if not integrated into workflow

Friedman CP. A "fundamental theorem" of biomedical informatics. *JAMIA*. 2009;16:169-170



To err is human.
A computer is required to really screw things up.

Introducing Knowledge into Decision Support Channels



American College of Medical Genetics and Genomics

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
Biotinidase deficiency (MIM 253260)	MedGen	BTD (MIM 609019)	ClinVar
Breast-ovarian cancer, familial 1 (MIM 604370)	MedGen	BRCA1 (MIM 113705)	ClinVar

Genomic Testing (Secondary Findings) ACT Sheet
RYR1 and *CACNA1S* Pathogenic Variants (Malignant Hyperthermia)

Known pathogenic or likely pathogenic variants (mutations) in the *RYR1* (ryanodine receptor type 1) gene or *CACNA1S* (muscle calcium channel) gene may result in familial malignant hyperthermia (MH), a condition triggered by exposure to certain drugs used in general anesthesia including inhalation anesthetics and succinylcholine. Some pathogenic variants in the *CACNA1S* gene cause a different condition, hypokalemic periodic paralysis.

YOU SHOULD TAKE THE FOLLOWING ACTIONS:

- Inform the individual (or parent/guardian) of the genomic screening result and high risk of malignant hyperthermia from general anesthesia.
- Obtain and review family and medical history. Evaluate the patient.
- Refer for genetic counseling.
- Patient needs to be instructed to inform the anesthesia team of high risk for malignant hyperthermia prior to any procedure requiring anesthesia.

Clinical Considerations: Malignant hyperthermia is a disorder in which affected individuals have few or no symptoms until exposed to volatile anesthetic gases and/or succinylcholine used in general anesthesia. Cardiovascular collapse and death can occur if not rapidly treated. Local anesthetics are considered safe. Rare individuals with malignant hyperthermia may become symptomatic with strenuous exercise or exposure to extreme heat. Treatment is to avoid exposure to the causative anesthetic agents, succinylcholine, or triggering environments. The screen-positive individual should inform the anesthesiologist/anesthetist of the presence of the variant prior to undergoing any general anesthesia. As many as 50% of those with malignant hyperthermia pathogenic variants may not develop malignant hyperthermia when exposed (nonpenetrance), however, the response to any given episode of anesthesia is unpredictable.

Mode of Inheritance: Malignant hyperthermia has an autosomal dominant pattern of inheritance. It is important that immediate and extended family members be offered genetic testing for malignant hyperthermia. Mutations in the *RYR1* gene are found in 70% - 80% of malignant hyperthermia cases while 1% involve the *CACNA1S* gene expressed in a skeletal muscle calcium channel.

Additional Information:

GeneReviews
Genetics Home Reference
ClinGen Actionability Report

Referral (local, state, regional and national):

Testing

"You Should Take the Following Actions" sections of ACMG ACT Sheets

Familial hypercholestero-lemia (MIM 143890)	• Inform the individual (or parent/guardian) of the genomic screening result and that there is a high lifetime risk of developing disease. • Obtain family and medical history and evaluate the patient. • Measure blood pressure, blood glucose, and lipid levels. • Refer for genetic consultation and counseling.
Lynch syndrome (MIM 120435)	• Inform the individual (or parent/guardian) of the genomic screening result and that there is a high lifetime risk of developing cancer. • Obtain and review family and medical history. Evaluate the patient. • Refer to gastroenterologist and gynecologist or gynecological oncologist for surveillance or and risk-reducing surgery discussion for endometrial and ovarian cancers. • Refer for genetic consultation and counseling.
Malignant hyperthermia (MIM 145600)	• Inform the individual (or parent/guardian) of the genomic screening result and high risk of malignant hyperthermia from general anesthesia. • Obtain and review family and medical history. Evaluate the patient. • Refer for genetic counseling. • Patient needs to be instructed to inform the anesthesia team of high risk for malignant hyperthermia prior to any procedure requiring anesthesia.

This Study: Methods

- For each ACGM disease/gene pair:
  - Reviewed MedGEN, GeneReviews and ACT sheets
  - Looked for authoritative recommendations (not just sensible suggestions)
  - Actions to be done *after* variant detection (not reason to do genetic testing)
- Analysis of recommendations:
  - Disease type (metabolic, anatomic, neoplastic, etc.)
  - Recommendation type (preventive, diagnostic, therapeutic, etc.)
  - Specific actions (testing, medication, surgical procedure, etc.)
  - Timing (immediately, certain age, frequency, etc.)

Sample Recommended Actions from GeneReviews and ACT Sheets

Recommendation Category	Condition Class	Specific Substance or Situation to Recommend or Avoid	Context and Comments
Agents/circum-stances to avoid	Cardio-vascular	flecainide, propafenone	All Class 1C antiarrhythmic drugs
Agents/circumstances to avoid	Cardio-vascular	Competitive sports	Immediate recommendation to patient
Agents/circum-stances to avoid	Drug Interaction	Dantrolene	should not be given with calcium channel blockers
Agents/circum-stances to avoid	Metabolic	liver, brain, chocolate, mushrooms, shellfish, and nuts	Dietary restriction on foods high in copper
Agents/circum-stances to avoid	Metabolic	Raw eggs	contains avidin that binds biotin
Agents/circum-stances to avoid	Neoplastic	living at high altitudes	hypoxic conditions
Evaluation of Relatives at Risk	Metabolic	p.Cys282Tyr	Molecular genetic testing to the adult siblings of a proband homozygous for p.Cys282Tyr to allow early diagnosis and surveillance.
Evaluation of Relatives at Risk	Structural	FBN1 pathogenic variants	genetic status of at-risk relatives of any age be clarified so that affected individuals can undergo routine surveillance for early detection of medically significant complications
Pregnancy management	Cardio-vascular	Aortic imaging	Increase frequency during and after pregnancy

Prototype knowledge table for genomic-guided decision support.

Condition	Gene	Variant	Inheritance	Evoke	Age	Action
Marfan's Syndrome	FBN1	15q21.1	Autosomal Dominant	Fluoroquino-lone Order	Any	Write "Avoid fluroquinolones in patients with Marfan Syndrome as they may exacerbate the predisposition for aneurysm and dissection."
Marfan's Syndrome	FBN1	15q21.1	Autosomal Dominant	Oral Decongestant Order	Any	Write "Avoid agents that stimulate the cardiovascular system, including decongestants and caffeine."
Marfan's Syndrome	FBN1	15q21.1	Autosomal Dominant	Outpatient Visit	Any	Write "Recommend annual echocardiogram."
Marfan's Syndrome	FBN1	15q21.1	Autosomal Dominant	Outpatient Visit	Any	Write "Recommend measurement of length/height/weight at each visit. Ophthalmologic examination annually or as clinically indicated...."
Marfan's Syndrome	FBN1	15q21.1	Autosomal Dominant	Outpatient Visit	18+	Write "Beta blocker or angiotensin receptor blocker is recommended to reduce hemodynamic stress on the aortic wall."
Malignant Hyperthermia	RYR1	19q13.2	Autosomal Dominant	Inhaled Volatile Anesthetic Order	Any	Write "Inhaled volatile anesthetics contraindicated; use diazepam, ketamine, midazolam, pentobarbital, propofol, or nitrous oxide."

Results: ACT Sheets

- 89 ACT sheets: 7 are relevant to 13 of the 73 actionable genes
- Five classes of conditions are related to the 73 actionable genes:
  - Cardiovascular diseases and abnormalities: 27 genes
  - Medication interactions: 2 genes
  - Metabolic conditions: 11 genes
  - Neoplasias: 28 genes
  - Protein structural abnormalities: 5 genes

Recommendation Classes

1. Actions or circumstances to avoid
2. Evaluation of relatives at risk
3. Pregnancy management
4. Prevention of primary manifestations
5. Prevention of secondary complications
6. Surveillance
7. Treatment of manifestations

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action:
write "You have ordered " || ordered_medication || " for your patient, " || patient_name ||
".\n\nThis patient has a variant at location " || Variant || " in gene " || Gene || " related to "
 || Condition || ".\n\nGenomic-guided precision management recommends: " || Action;
;;
end:
```

Medication-Genome Interaction Alert

You have ordered levofloxacin for your patient, John Johnson.

This patient has a variant at location 15q21.1 in gene FBN1 related to Marfan's Syndrome.

Genomic-guided precision management recommends: Avoid fluroquinolones in patients with Marfan Syndrome as they

Click H

John Johnson has the following actionable genetic variants (click on each to learn more):

- Condition: Malignant Hyperthermia, Gene: RYR1, Location: 19q13.2, Recommendation: Inhaled volatile anesthetics contraindicated; use diazepam, ketamine, midazolam, pentobarbital, propofol, or nitrous ox
- Condition: Malignant Hyperthermia, Gene: RYR1, Location: 19q13.2, Recommendation: Recommend gen screening for family members.
- Condition: Marfan's Syndrome, Gene: RYR1, Location: 19q13.2, Rrecommendation: Avoid fluroquinolone patients with Marfan Syndrome as they may exacerbate the predisposition for aneurysm and dissection.

Discussion

- Big Data + Machine Learning = Big Knowledge
- A little knowledge is a dangerous thing
- Too much knowledge is paralyzing
- Fundamental informatics research is needed to:
  - Integrate knowledge efficiently (including maintenance)
  - Make the workflow work for us, not against us

Cimino's Corollary to Friedman's Fundamental Theorem