

Tissue and Data Banking

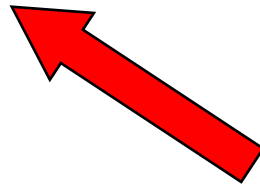
An Essential Ingredient for Genetic Research

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- The Secretary of Health and Human Services Mike Leavitt has made personalized medicine the top priority during his tenure.
- And created the Secretary's Advisory Committee on Genetics, Health and Society aka SACGHS.

Agenda

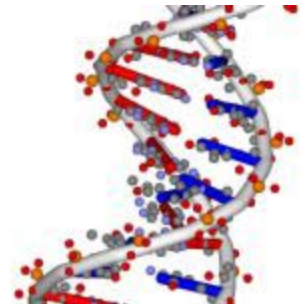
- What is personalized medicine?
- Why it Depends on Tissue and Data Banking
- The Logistics of tissue and data banking
- Informed consent for tissue and data banking
- The gnarly issues

Personalized Medicine

What is it?

- The use of “information about a person’s genetic makeup to tailor strategies for the detection, treatment, or prevention of disease.”

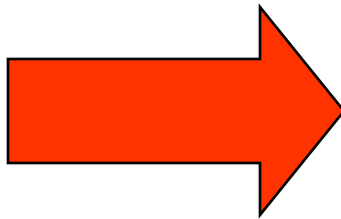
Francis Collins: Boston Globe July 17, 2005



Personalized Medicine

What is it?

- Pharmacogenomics: the effect of an individual's genes on the response to drugs



Wikipedia

- **Personalized medicine** is the use of detailed information about a patient's genotype or level of gene expression and a patient's clinical data in order to select a medication, therapy or preventative measure that is particularly suited to that patient at the time of administration.

What is it not



Personalized Medicine

Generic Approach

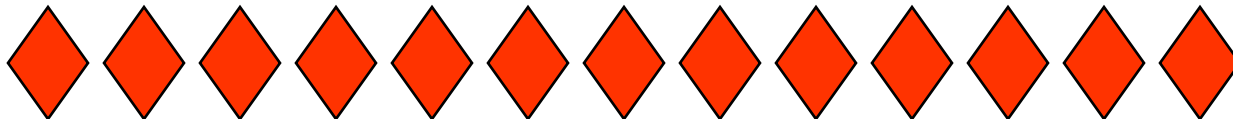
- Identify specific genetic footprint of a particular disease/condition/tumor
 - Design therapeutic regimen that specifically attacks that footprint
 - Create reliable 'test kit' (theranostic) for clinical use
- Identify metabolic profile
 - Develop a reliable 'test kit' (theranostic) for clinical use
 - Design dosing regimen that respects individual metabolic profile

Personalized Cancer Care

- Identify the target cancer (TC) 
- Obtain tissue specimens
 - Ideally develop a tissue bank of all persons with Target Cancer. Bank will include:
 - Tissue specimen/s
 - Demographics and longitudinal medical information that is continuously updated
 - Therapeutic response
 - Tumor progression/regression

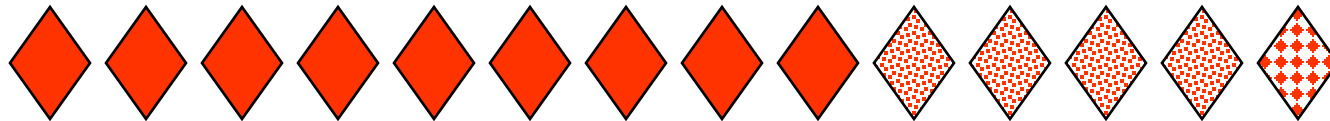
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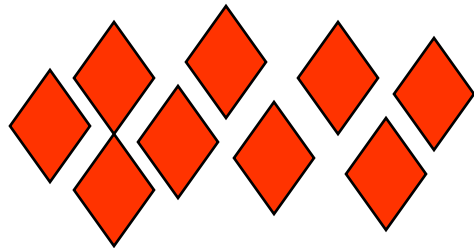
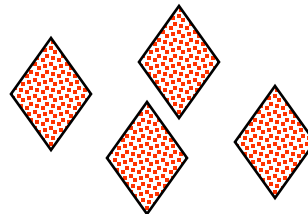
Personalized Cancer Care

- Sub-populations will emerge:
 - Response to specific therapy/ies
 - Progression of the cancer
 - Morbidity as well as mortality
 - Demographics and co-morbidities



Personalized Cancer Care

- Study sub-populations to find any distinguishing tumor characteristics – e.g. genetic identifiers, that relate to response to therapy and/or outcome
- Focus drug research on these distinct sub-populations



Personalized Cancer Care

New patient

- At time of diagnosis, patient/tumor undergoes genetic testing for assignment to any identifiable subpopulation
- Therapy designed for the appropriate sub-population is administered
 - After the patient's genetic footprint re: drug metabolism is completed

Personalized Cancer Care Success Story

- New patient gets:
 - Only drug/s that is/are effective for his/her own tumor
 - Drug dosing that matches his/her drug metabolism profile
- Increased survival
- Decreased morbidity

Herceptin (Trastuzumab)

- Acts on HER-2/neu receptor
 - 25-30% Breast Cancers have amplification of HER-2
 - Increased invasiveness and drug resistance
- September 25, 1998
 - FDA gave simultaneous approval for:
 - Herceptin (Genentech)
 - HercepTest (DAKO)
 - FDA approved label for patients over-expressing Her2

Purine Metabolism

- 85 percent of children with acute lymphoblastic leukemia cured with 6-mercaptopurine (6-MP)
 - BUT drug-associated mortality.
- 1 in 10 individuals has an under-active version of the metabolizing enzyme thiopurine S-methyltransferase (TPMT) and should receive lower doses of purine drugs.
- Physicians now screen for TPMT gene variants before administering these drugs.

Personalized *Common* *Condition* Care

- Common, multi-factorial conditions; e.g., hypertension, asthma
 - Multiple subgroups
 - More subtle outcomes
 - *Study will require thousands of subjects*

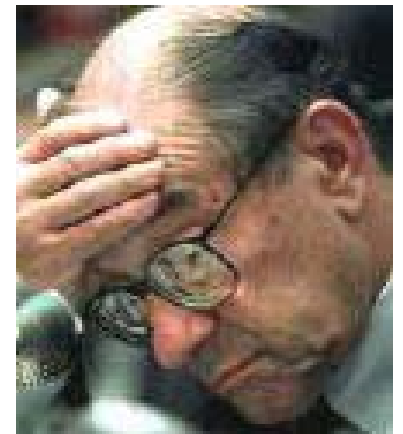
Personalized Medicine

What must be done to achieve it.

- **Large tissue/data banks**
 - Links to each individual's:
 - Existing demographics
 - Existing medical information
 - Updates with:
 - Any changes in individual's demographics
 - New medical information
 - Possibly with any research results

Challenges of Banks

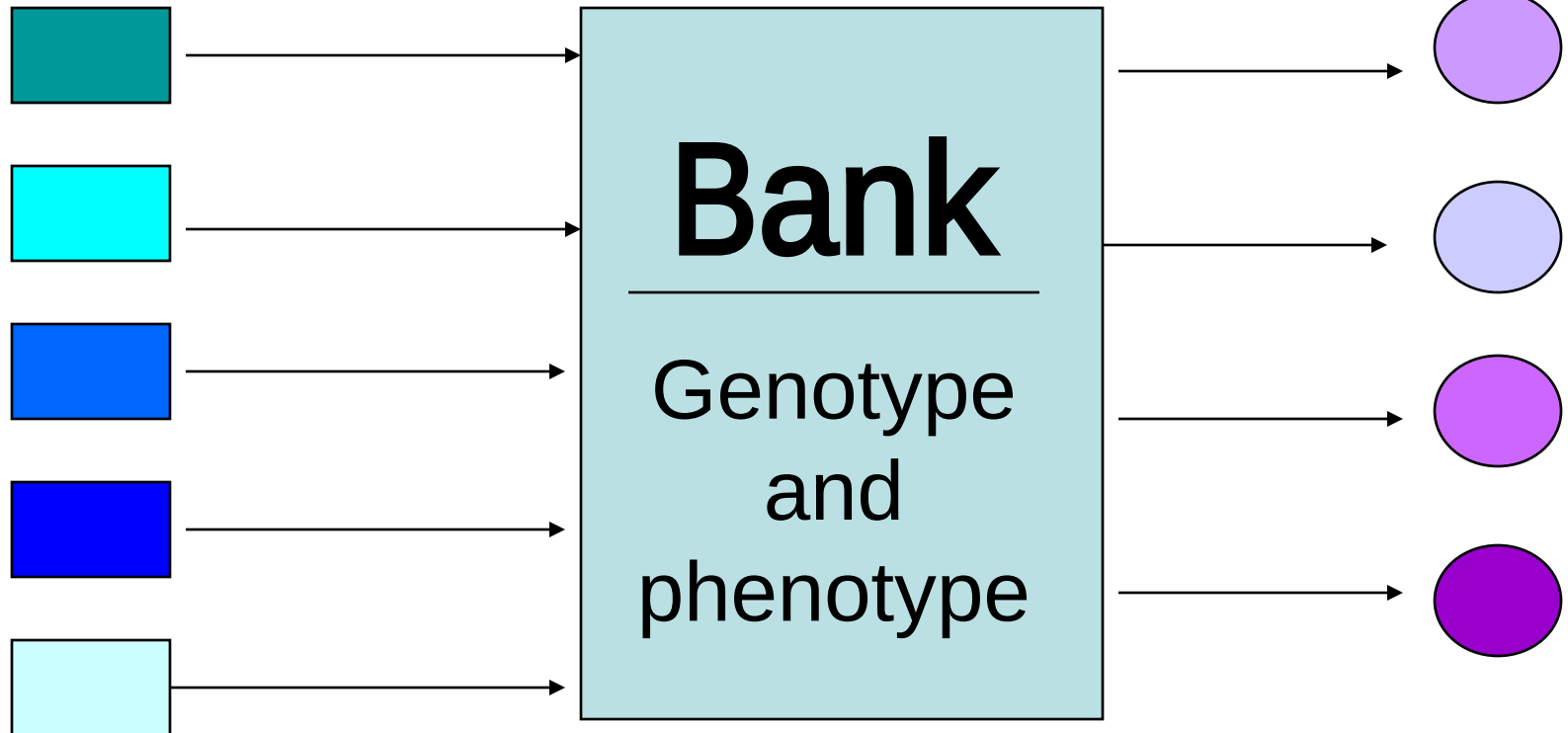
- The logistics of setting up and maintaining large tissue/data banks
 - IRB Issues:
 - Common Rule and FDA regulations
 - HIPAA – Privacy and Security Rules
 - Information systems
 - Funding



Bank Model

Submitting
investigators

Recipient
investigators



Bank Model





Identifiable data?

Quality control

Rules of operation

Who can submit

Who can access



How was data obtained?

Informed consent?

Submission

Identifiable?

Coded?



How to access

Ethical review

What can be accessed

What to do with results

Stakeholders

Benefits and Challenges

- **Patients**
- **Researchers**
- **Industry**
- **Payers**

Benefits and Challenges

Patients

- Benefits
 - Ability to identify predilection for disease
 - May be able to avoid disease progression
 - Exposure to drugs that will be beneficial
 - Minimize exposure to ineffective drugs
 - Drug dosing that meets patient's metabolism profile

Metabolomics

- “Paxil (paroxetine) is metabolized through CYP2D6. Pharmacogenetic testing of this pathway serves as an anchor for the intense personalization required to effectively prescribe Paxil and other antidepressants.”

<http://www.healthanddna.com/professional/paxil.html>

Benefits and Challenges

Patients

- Challenges
 - Privacy concerns with large tissue banking that is needed to support development of 'personalized medicine'
 - Incentives for participation vary by disease
 - Concerns of discrimination based on:
 - Potential for life-threatening disease/condition
 - More aggressive sub-group of common diseases
 - More 'expensive' common disease

Metabolomics

- Hospitalized psychiatric patients who are poor metabolizers cost \$4,000 - \$6,000 more in medical care compared to patients with an average metabolizer genotype. Virtually, all antidepressants and antipsychotic medicines are processed by enzymes with a high incidence of poor metabolizers.

Benefits and Challenges

Researchers

- Benefits
 - The ultimate opportunity for translational research
 - More focused research on specific disease/s
 - Potential to pre-identify poor responders that would negatively affect the overall safety and efficacy data

Benefits and Challenges

Researchers

- Challenges
 - The logistics of large data and tissue repositories
 - May have to create their own
 - Recruitment and consent of large numbers
 - Management of large repositories
 - May be under the ownership/control of others
 - Accepting 'rules' of another's bank
 - Intellectual Property and 'Credit'

Benefits and Challenges Industry

- Benefits
 - Focused, more efficient drug development
 - Less investment
 - Less elapsed time
 - Availability of therapeutic with relevant theranostic test could increase consumer loyalty

Example of Potential Benefit

- 1998 FDA forced market withdrawal of Seldane (Terfenadine):
 - Small number developed severe cardiotoxicity
 - Less than 0.5% of population has a variant CYP3A gene which makes them unable to metabolize Seldane in the presence of erythromycin
- What if drug was marketed with a theranostic for CYP3A genetic variant?

Benefits and Challenges

Industry

- **Challenges**

- Concept of Block Buster drug development and marketing brought into question
 - Catering to small subpopulations of wealthy conditions
 - Threat to existing Block Busters
 - When generics do as well as patent drug in most, but not all cases; genetic test may be able to identify the few who need the more expensive drug
 - How to finance the development of specific drugs for relatively small sub-populations
- Diagnostic kit development – who will do this?
 - Does this change liability?

Benefits and Challenges

Payers

- Benefits
 - Decreased use of ineffective drugs
 - Increased use of effective drugs and safe dosing
 - Decreased drug toxicity and side effects
 - While cost per unit may be higher, overall cost of health care may decrease

Benefits and Challenges

Payers

- Challenges

- Will drugs be more expensive?
- How to cover prevention strategies?
- How to consider genetic tests and/or diagnostic kits?
 - Required for coverage?
 - If not required, reimbursed?
 - Will coverage rates be affected?

Cost of Herceptin

- Most journals quote: \$3,000/month
- Genentech reports approx \$2500/infusion vial
- Patient reports:
 - Hospital 1: \$6,254.95/infusion
 - Hospital 2: \$9,599.10/infusion – same dose
 - Insurance pays: \$4,635.00/dose

http://www.assertivepatient.com/2007/03/the_true_cost_o.html

Cost of Herceptin

- The real cost of Herceptin is borne by other patients whose treatment has to be dropped to balance the books.
- Three hospitals figured:
 - Herceptin cost 4 times adjuvant therapy costs
 - Need 1.9m pounds/year to treat 75 eligible patients
 - 2.3m pounds/year including testing and monitoring
 - Options:
 - Stop treating 355 patients receiving adjuvant care
 - 16 of whom will be cured
 - Discontinue palliative treatment on 208 patients

Some Gnarly Issues

- Is genetic data ever truly not identifiable?
- What is adequate consent?
 - How to consider pedigrees
- How will risk of future use be assessed?
 - By whom?
- Pediatric specimens
- How to handle community consent
- What to do with results
- How to protect against nefarious uses of data

Identifiability

- Have we crossed the threshold into identifiability?
 - “...composite statistics across cohorts, such as allele frequency or genotype counts, do not mask identity within genome-wide association studies.”
 - Homer et al: Plos Genetics 2008:4:1-9

Adequacy of Consent

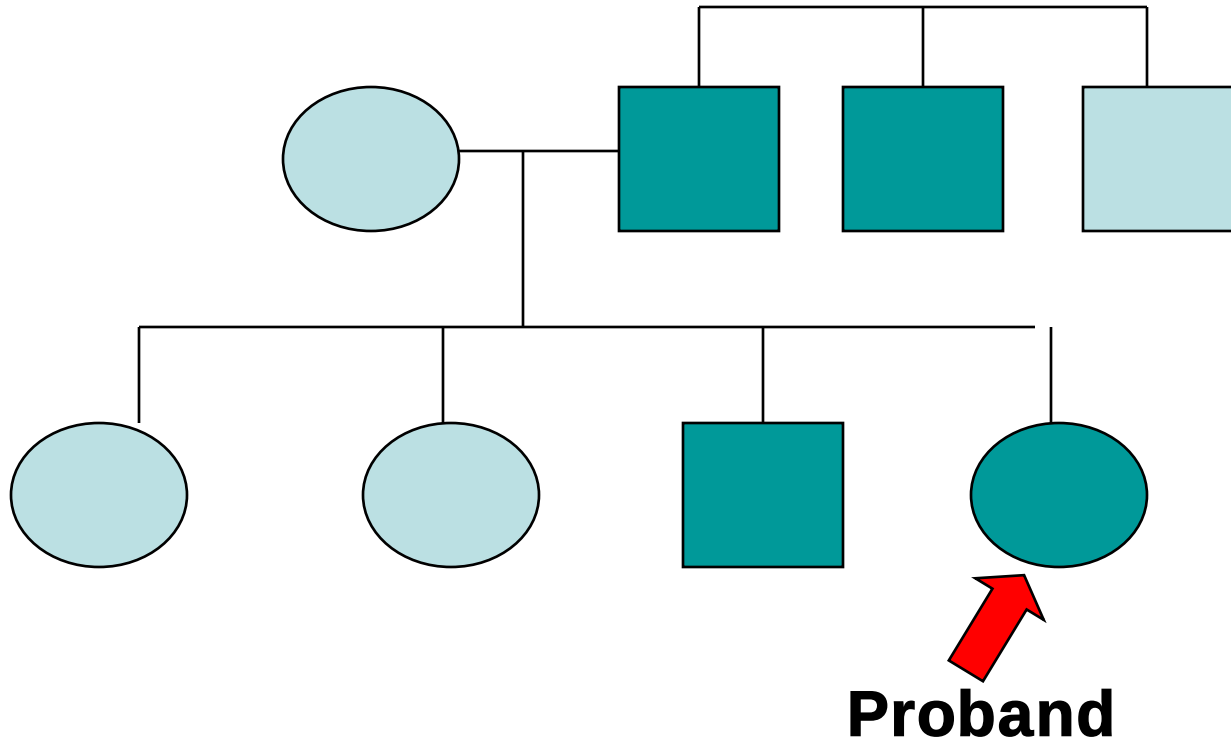
- How to describe genetics
- How to describe banking
- What is the benefit
- What is the risk
 - Physical – small
 - Psychological and privacy
- Who should give consent?

Informed Consent for Genetic Research

Hamvas et al. Arch Ped Adol Med 2004;158:551-5

- 465 families approached – genetic study of IRDS
- 135 families refused:
 - 79% stated language in consent suggesting potential denial of access to insurance or employment
 - 20% stated not enough time

Who is a subject?



Who is a Subject?

- **YES**
 - Daisy Mae
 - Mother of Daisy Mae
- **No**
 - Ageless woman in cartoon strip
 - Mother of ageless woman in carton strip

Difficult Populations

- Children
 - Include or exclude
 - Re-consent at age of majority?
- Decision-impaired persons
- Communities at risk

Return of Research Results

- In favor
 - Respectful of participants
 - May be valuable information
- Against
 - Chain of custody often questionable
 - Validity and utility of results
 - Need for appropriate support

Personal Genome Project

George Church: Harvard University

- Aim: to publish the genotype (full DNA sequence), extensive phenotypic information, medical records, various measurements, MRI images, etc.
 - All data will be freely available over the Internet, so that researchers can test various hypotheses about the relationships among genotype, environment and phenotype
- Data will be linked to volunteers by name (since full anonymity can never be guaranteed anyway).
 - A secondary aim is the exploration of the resulting risks to the participants, such as possible discrimination by insurers and employers if the genome shows a predisposition for certain diseases.

Personal Genome Project

George Church: Harvard University

- Harvard Medical School IRB requested that the first set of volunteers include the PGP director and other diverse stakeholders in the scientific, medical, and social implications of personal genomes, because they are well positioned to give highly informed consent.
- Ultimately volunteers from all walks of life will be asked to participate.
 - Question: How to ascertain fully *informed* consent

Personal Genome Project

George Church: Harvard University

Risks Listed on the Website

- Infer paternity
- Employment and/or insurance discrimination
- “Claim relatedness of the volunteer to infamous villains”
- “Make synthetic DNA corresponding to the volunteer and plant it at a crime scene”
- Revelation of a disease lacking a current cure
- Risks to family members

Final Thoughts

- The potential benefits of personalized medicine are extraordinary
- The logistics of developing and maintaining the requisite tissue and data banks are daunting
- Anti-discrimination legislation will always be faulty
- Even good data can be put to nefarious uses

Final Thoughts

- True protection of privacy and confidentiality may not be possible

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- Not all information will be welcomed

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