Ethical Challenges In Analysis of Archived Biospecimens from Past Clinical Trials

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Theoretical Case

- We discover a new biomarker of response to taxane therapy in lung cancer (MWO)
  - Microtubules watch out!
- We want to know if expression of MWO can guide choice of therapy for breast cancer
- We have trial with archived biospecimens…
  - Tumor blocks

Theoretical Case:

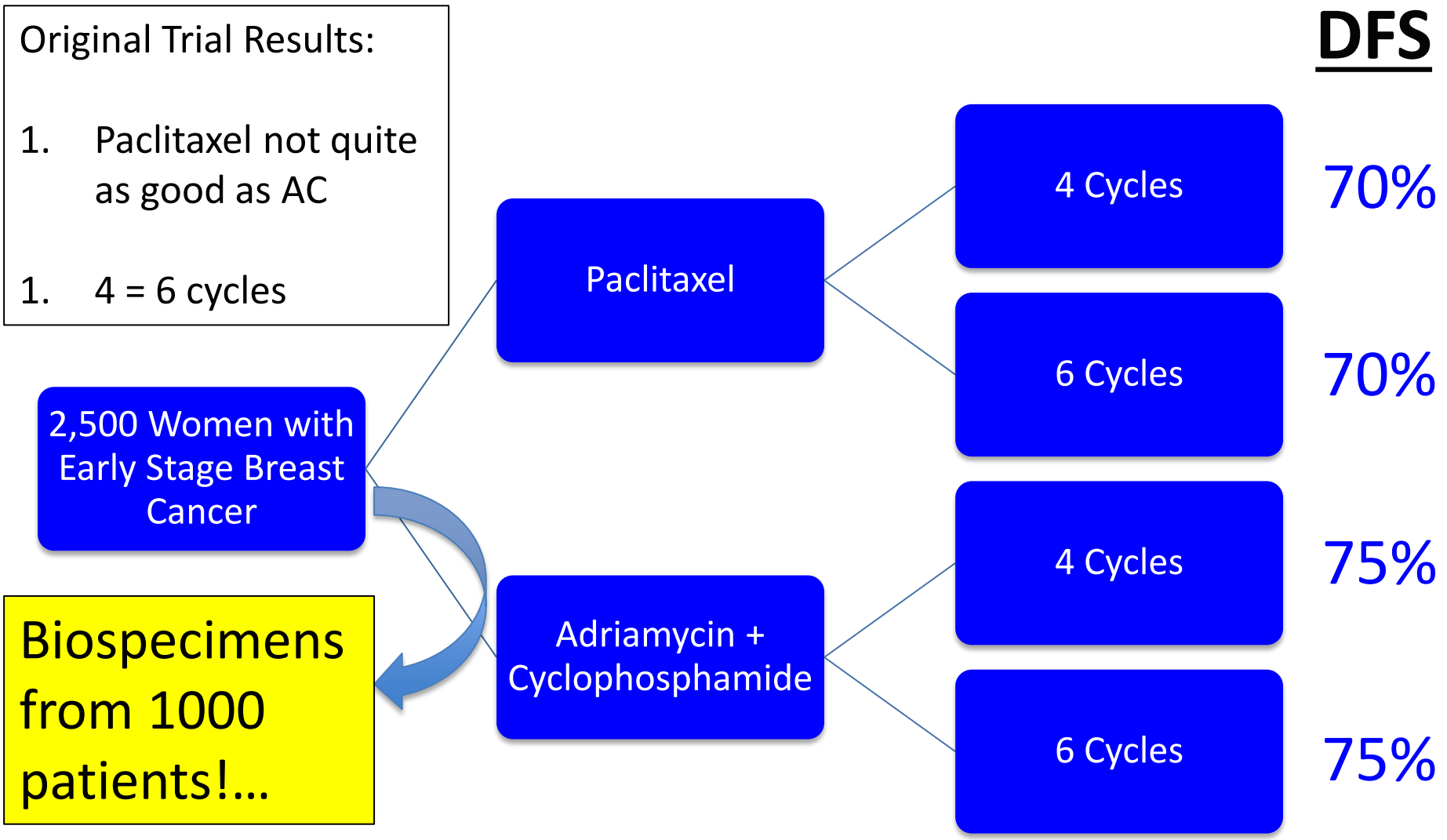
Use of Archived Biospecimens

10 year follow-up!

Original Trial Results:

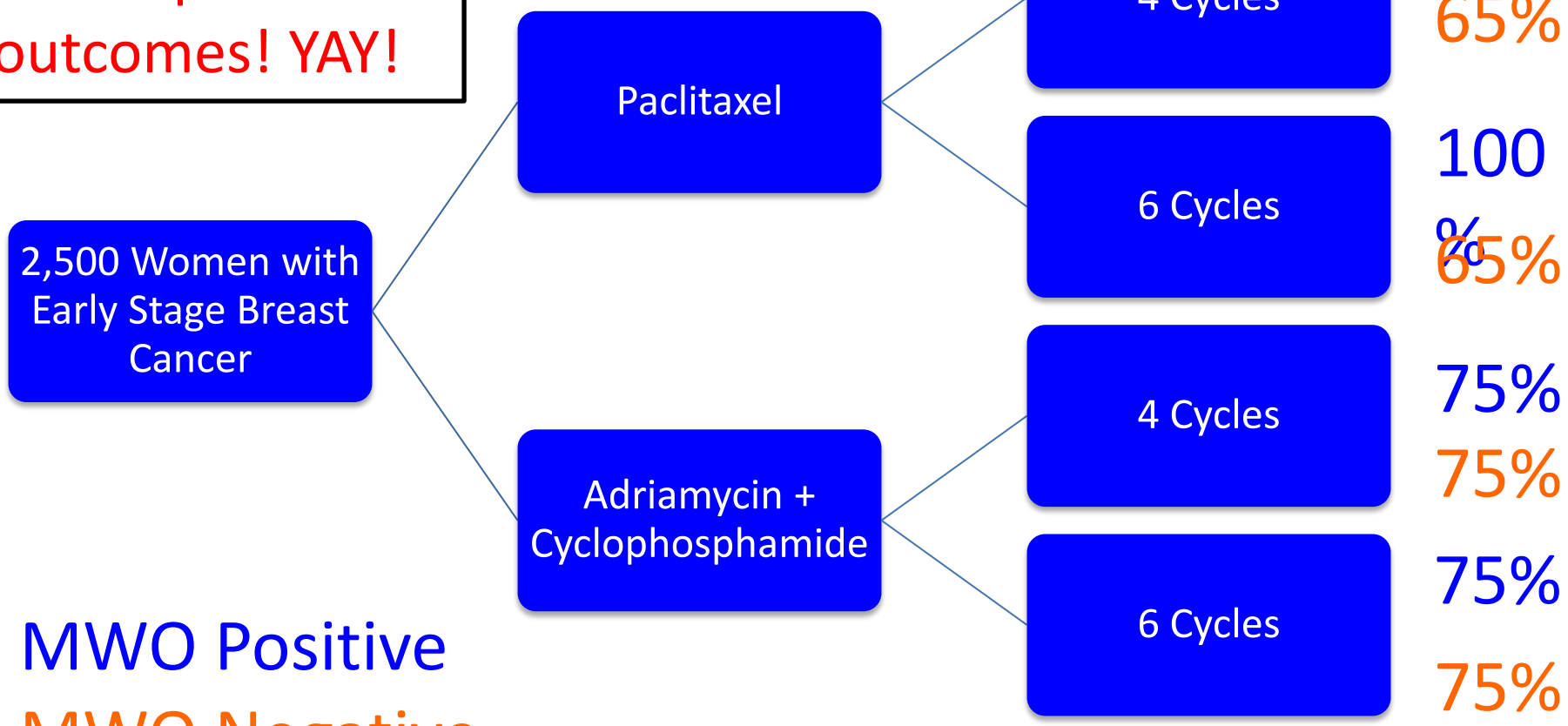
1. Paclitaxel not quite as good as AC

1. 4 = 6 cycles



Can We Find out if MWO Predicts Response in Breast Cancer?

This biomarker transforms care and improves outcomes! YAY!



BUT…..

- What if informed consent is inadequate?
  - Does not describe the current purpose (other diseases)
  - Does not specifically mention the technology (genetics)
  - Mentions tumor genetics (somatic) not inherited (germ line)
  - Does not describe the risks (privacy, discrimination)

    - Risks include giving others information about the individuals disease status, current or future traits, ethnicity, parentage

Other Options?

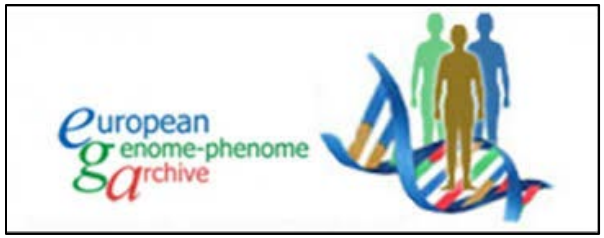
A. Organize a new 2,000 + person trial, give one group what is now considered inferior therapy…. And wait 10 years for results….

B. Collect new research biopsies from patients treated outside of trials with Regimen A or B (although B is now rarely used) and try to “learn radidly”

C. Decide some questions just can’t be answered.

D. Other ideas??

Brave New World



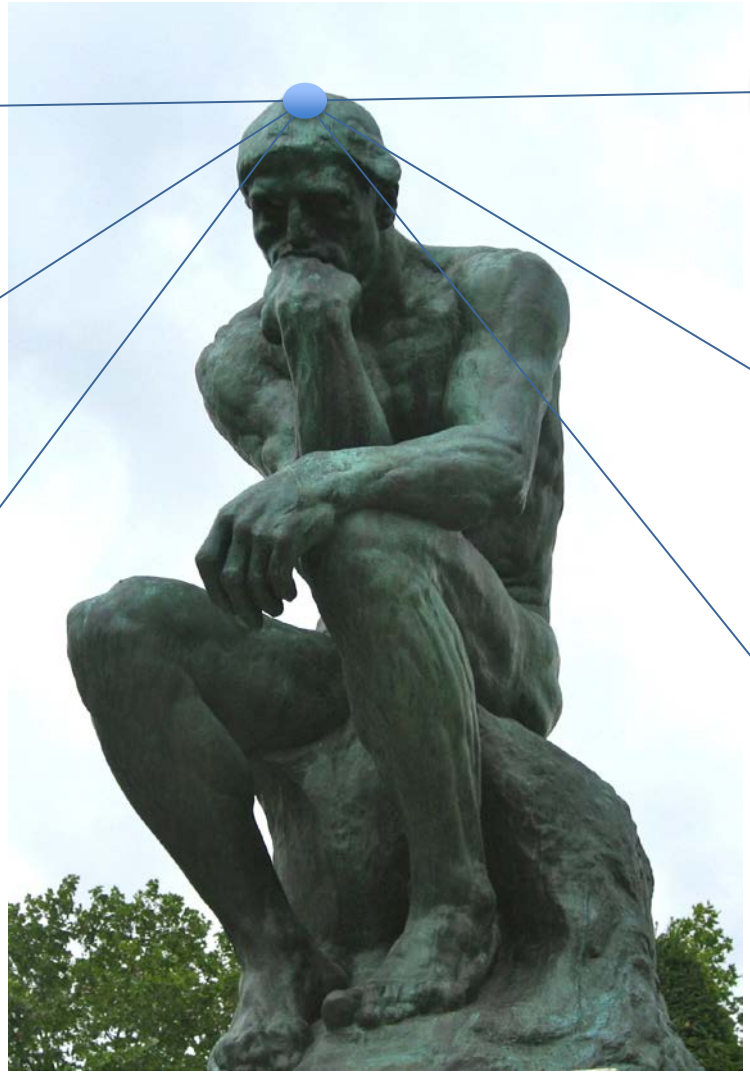
Human Genome Project = $2.7 Billion

Complete Genomics = $5,000

"Cheap" whole genome sequencing, data sharing, international collaboration

Kaye, Ann Rev Gen Hum Genet 2012

“Ideal” Informed Consent

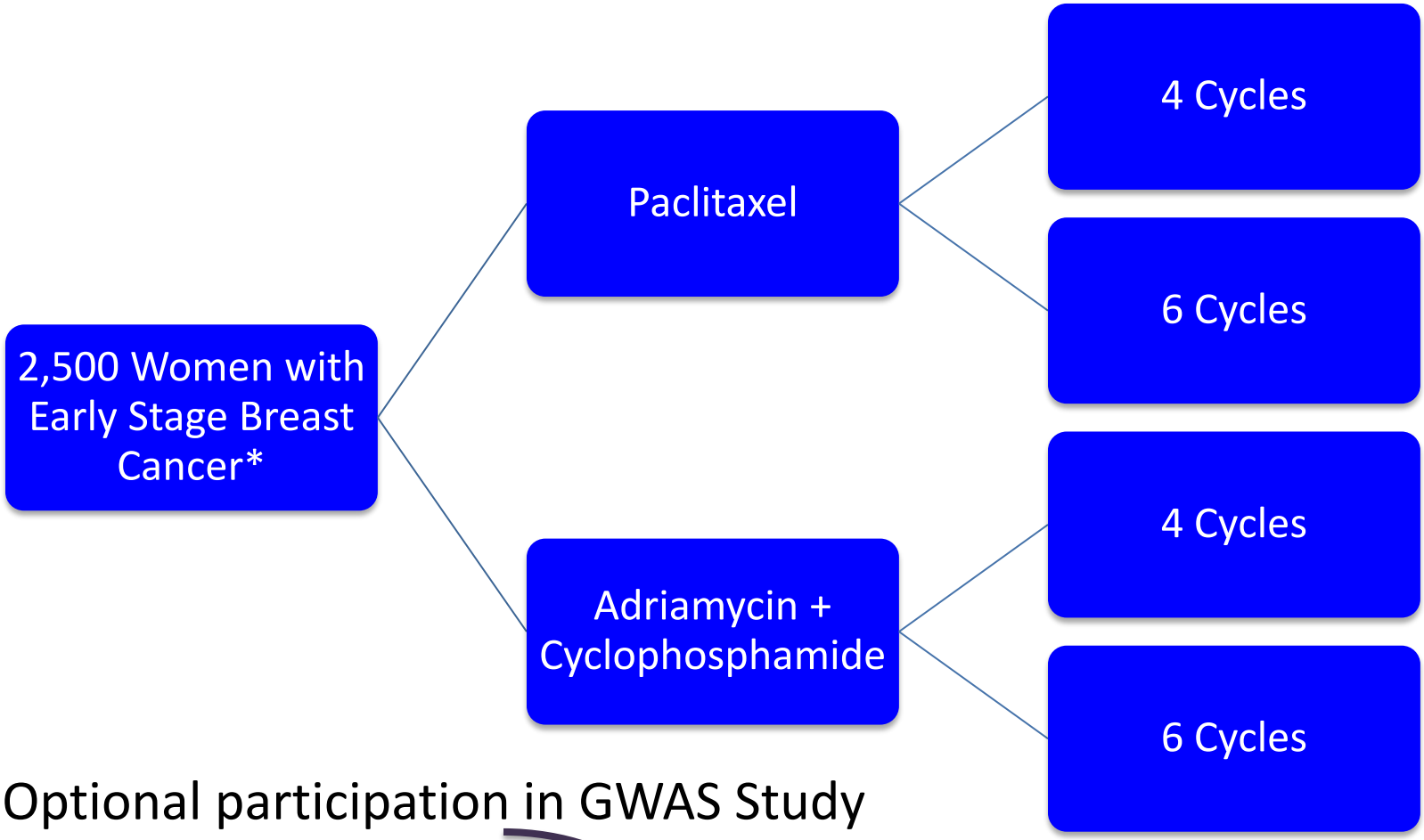


- Rationale
- Details of Study
- Possible Societal Benefits
- Likely Harms
- Any Direct Benefits
- Potential Risks

Challenge

- Biospecimens from older generation of trials did not use todays language
  - To explain genetics
  - To explain limitations of de-identification
  - To describe data-sharing
  - To explain potential privacy risks
  - To describe uncertainty
- BUT biospecimens were provided to help advance science, help future patients
  - Public Trust cuts both ways

Example 1: CALGB 40101



*Optional participation in GWAS Study

Can this be shared with dbGaP?

CALGB 40101

- Study initiated before dbGAP….

Informed Consent Document:

Did	Did Not
• Participation is voluntary • Discuss future genetics and pharmacogenetics research in general terms • Discuss uncertainty regarding details of future research questions • Promise CALGB review of any future research	• Use the words “genetics” or “genetic information” • Mention sharing geentic or clinical data with national database • Mention privacy risks • Mention potential for recontact

To Reconsent or Not to Reconsent?

Consent	Do Not seek Reconsent
• Adjuvant Trial • Majority of participants alive & recurrence free • Consistent with ideal of informed consent	• Expensive • Logistically difficult • May upset some who have experienced adverse outcomes • Bias to the Scientific Sample

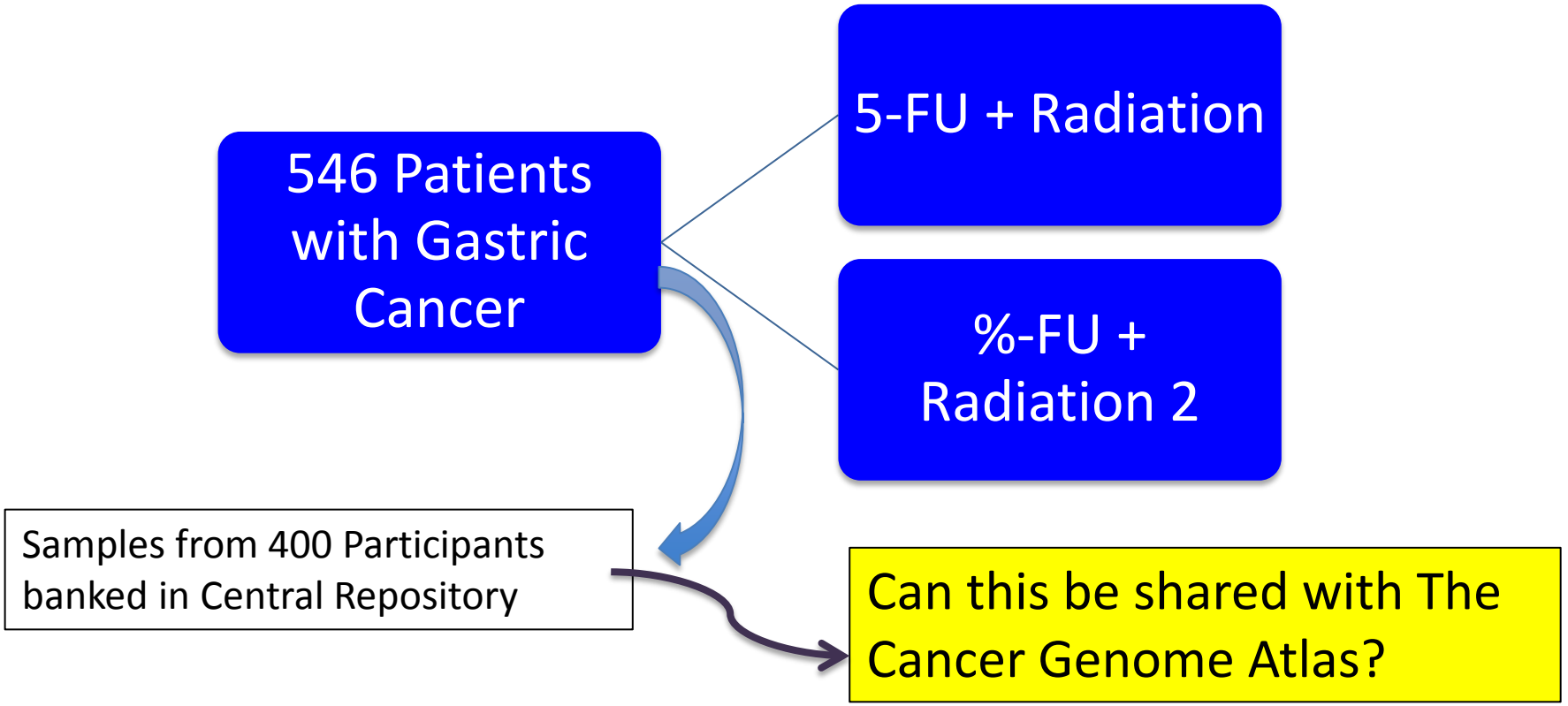
Key Considerations

- Potential societal benefit from sharing data?
- Was there informed consent for future research?
- Was uncertainty of risks from future unspecified research explained in the consent form?
- Is data sharing consistent with the goals and terms of the initial consent form?
- Is reconsent feasible?
- **Will the expressed interests of the participants be better honored through data sharing or withholding data?**

Peppercorn et al. Cancer. 2012 Oct 15;118(20):5060-8.

Example 2: CALGB 80101

Phase III Intergroup Trial of Adjuvant Chemoradiation After Resection of Gastric or Gastroesophageal Adenocarcinoma



"Given no pre-operative therapy, the tissue specimens from this trial represent a unique and unprecedented resource for a comprehensive molecular characterization of gastric and GE junction adenocarcinoma."

- CALGB Investigator

TCGA Guidelines:
Informed Consent Documents must explain…

- Some description of genetic or genomic research.
- The concept of data sharing, in broad terms
  - use by individuals other than the PI for the original project.
- The possibility of future research
  - research beyond cancer research,
  - research that may result in commercial products
- The risk of loss of privacy and confidentiality.
  - Measures taken to reduce risks should be described.

Informed Consent Document

- *"We would like to study cells from your tumor, for research only, we will not study inherited genes"* ☑ I Agree that my tumor may be used….
- "…whether substances in your blood (sometimes called tumor markers) are related to the way that your body responds (or doesn't respond) to the chemotherapy you receive in this trial. These tumor markers are inherited through your family, and could be passed to your children. These are also called genetic studies…" ☑ I Agree that my blood may be used….
- ☑ I agree that my DNA may be kept for future use in future DNA research studies to learn more about cancer.
- ☑ My tissue/blood may be kept for future unknown use in research to learn about, prevent, treat, or cure cancer.
- ☑ My tissue/blood may be kept for research about other health problems (for example: diabetes, Alzheimers, heart disease)

Alliance for Clinical Trials in Oncology

Alliance Ethics Review

- Study was open at >500 sites
- Did not use central IRB
- NOT possible to approach individual sites to approve use of specimens for TCGA
- The study team and ethics committee agreed that intent of participants who answered YES to all 5 questions in the ICD pertaining to future use of specimens was consistent with the TCGA

312 Participants with Adequate Consent

Summary

- What can we say about the future?
- We can predict with confidence that we will not be able to predict the questions we will want to ask or the technologies that will be available to answer them in the future….

Issues to Address

- Transparent and multidisciplinary process for reviewing use of archived biospecimens
  - Research?: What do patients/participants think?
- Legal protections to minimize risk of discrimination and abuse
  - Health and life insurance, gov't, workplace
  - Criminal penalties for hacking/stealing genomic data
- Prospectively, improve informed consent for future unspecified research
  - Focus on explaining uncertainty
  - Given broad scope of science, broad consent is best