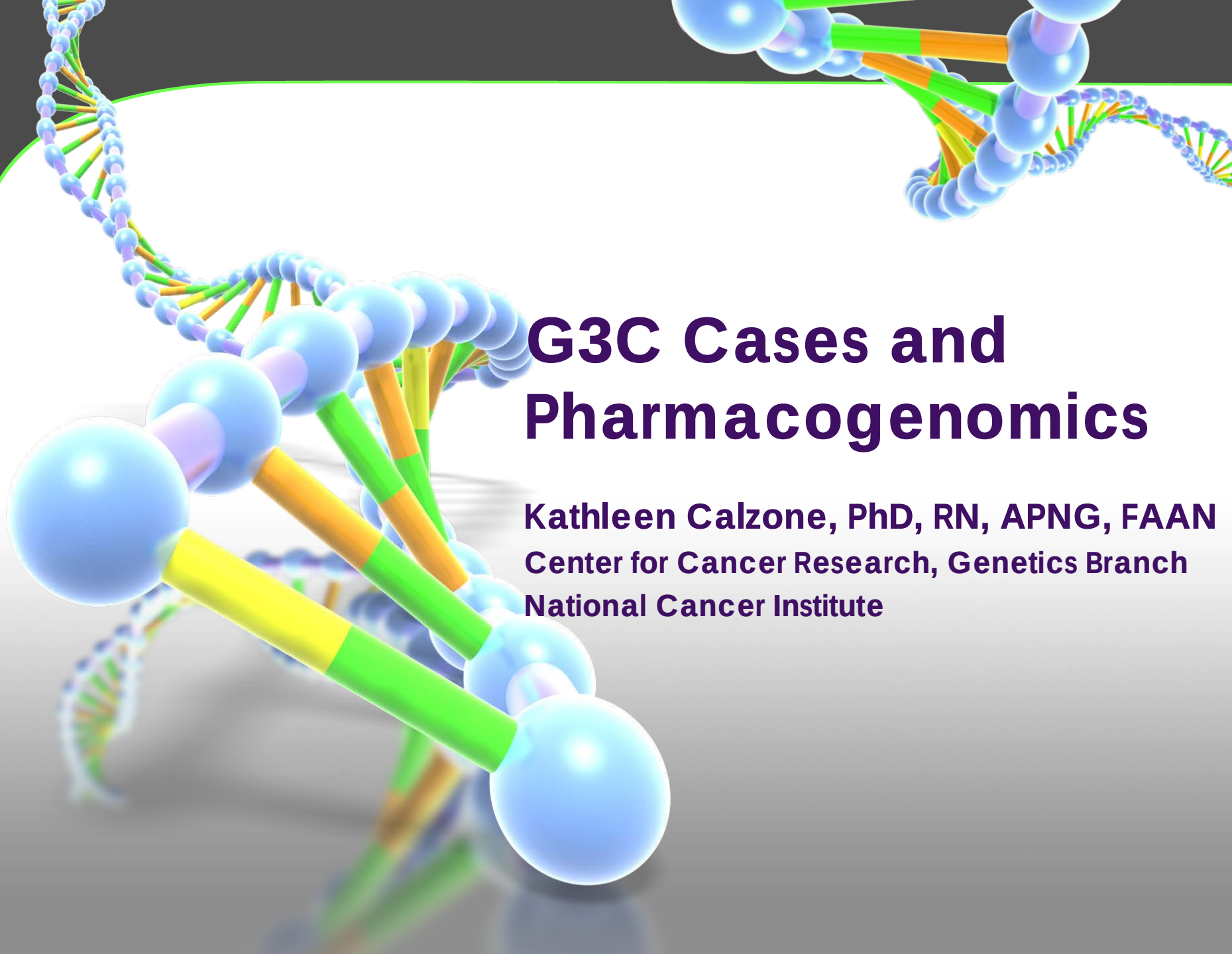


G3C Cases and Pharmacogenomics

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

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
- Bilingual (English/Spanish)
- Interactive, self-paced, self-directed, unfolding case studies

http://www.g-3-c.org

Global Genetics and Genomics Community (G3C)

- 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://www.g-3-c.org

Cases

16 cases available

Ethnically diverse

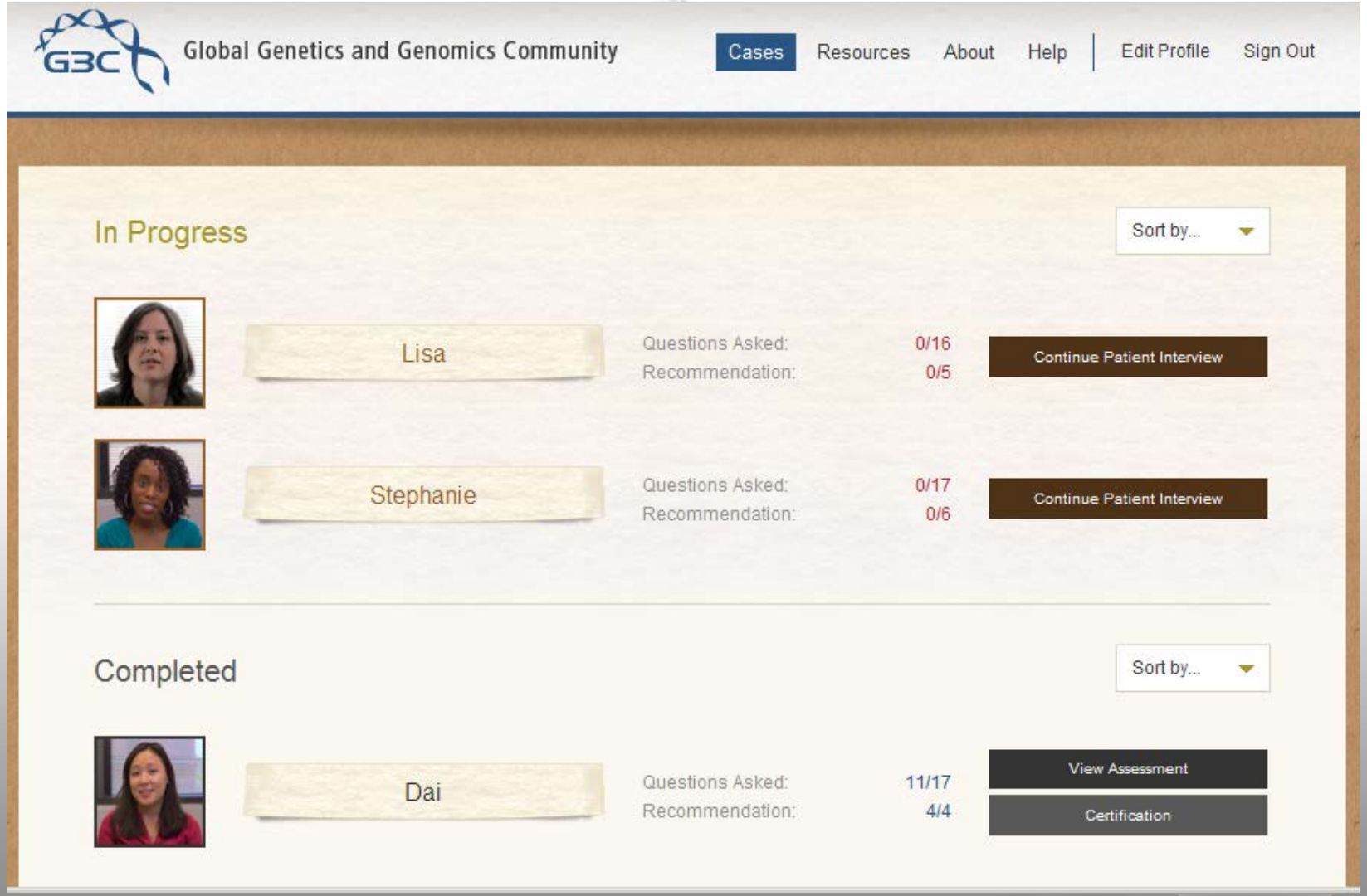
In- and Out-patient

Address

- Family history assessment
- Direct to consumer marketing/testing
- Family issues
- Personal values assessment
- Genetics/genomics of common diseases (diabetes, cardiovascular disease, psychiatric disorders, pharmacogenomics, prenatal testing)

Continuing Education Platform

Track Your Case Progress or Resume A Case



Filter Cases Based on Topic and/or Difficulty

FILTER BY

Select a Category

Select a Difficulty

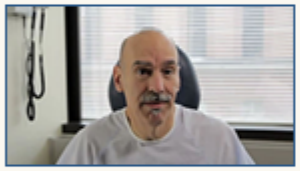
Case Studies

Start Case Study

View Case Notes

Gabe (View Patient Info)

Gabe Geller is a 55 year old Ashkenazi Jewish male who presents for evaluation of rectal bleeding and to receive his colonoscopy results. Several weeks ago he noticed a small amount of blood in the toilet bowl after a bowel movement. He thought it was just hemorrhoids and was not concerned. This happened a couple more times over the next few days and he mentioned this to his wife, who called to schedule him an appointmentt for evaluation about two weeks ago. He was referred to a gastroenterologist for a colonoscopy prior to this visit, which he had a few days ago. Eleven adenomatous polyps were found during the procedure, mostly on the right side of the colon. All polyps were successfully removed during the colonoscopy.



Start Case Study

View Case Notes

Gabe #2 (View Patient Info)

Gabe is a 56 year old Ashkenazi Jewish man who was recently admitted to the hospital for an arrhythmia. He is miserable having to stay in the hospital to be monitored and he is short with everyone. Work-up may indicate that he needs anticoagulation treatment and he is asking a lot of questions about what that means for him and his family.

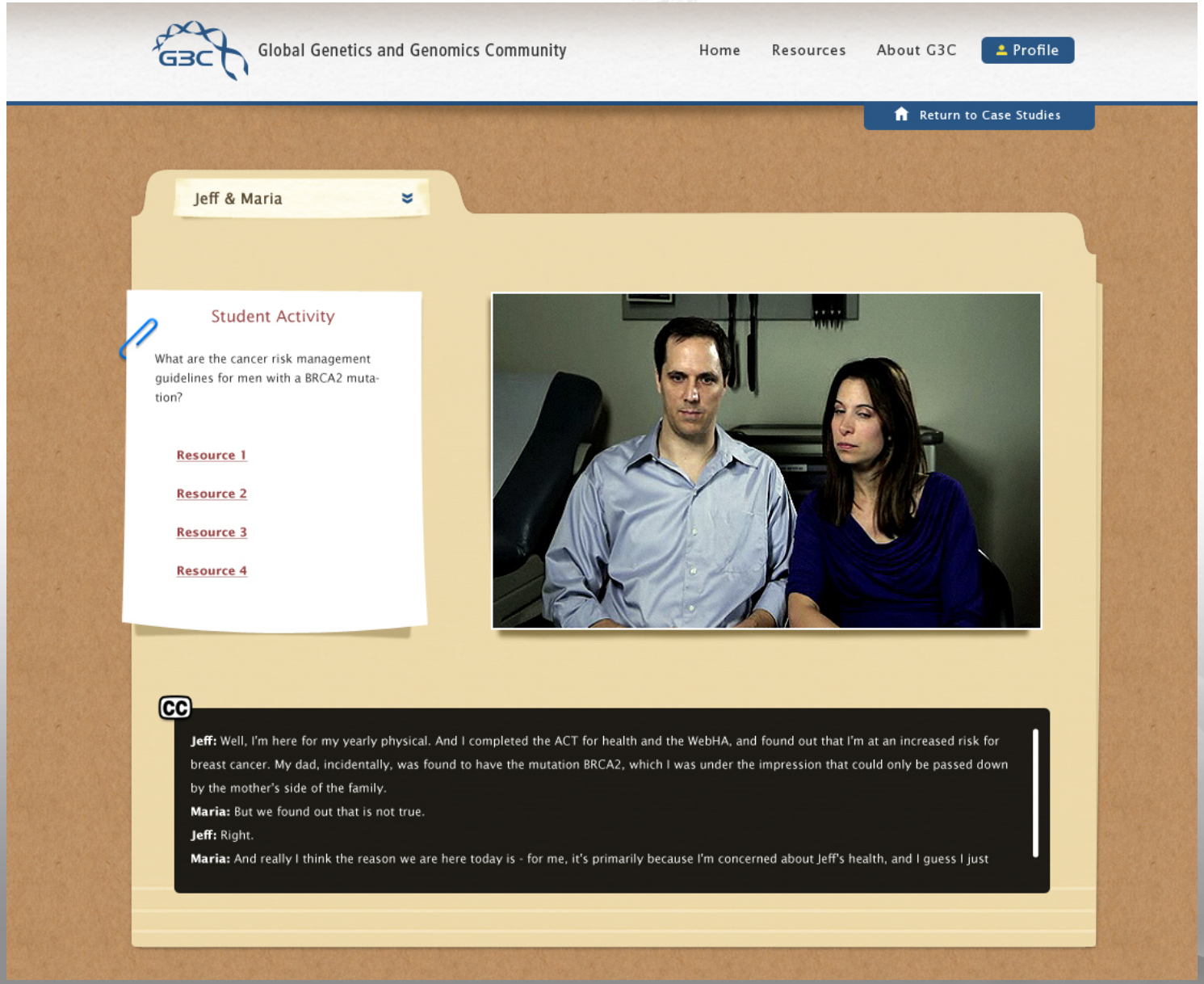
Start Case Study

View Case Notes

Grace (View Patient Info)

Grace Washington is a 44 year old African American female who moved to the area about a year ago and was referred to our clinic for her annual well woman examination. She has not seen a health care provider since her move. She is married with three children, reports having a family history of breast cancer and wants a mammogram because she is very concerned about her breast cancer risk due to her family history. A brief health history was taken by phone when she called to schedule an appointment as a new patient. A family history questionnaire was emailed to her and she completed it and brought it with her to the clinic visit.

Case Format


Global Genetics and Genomics Community
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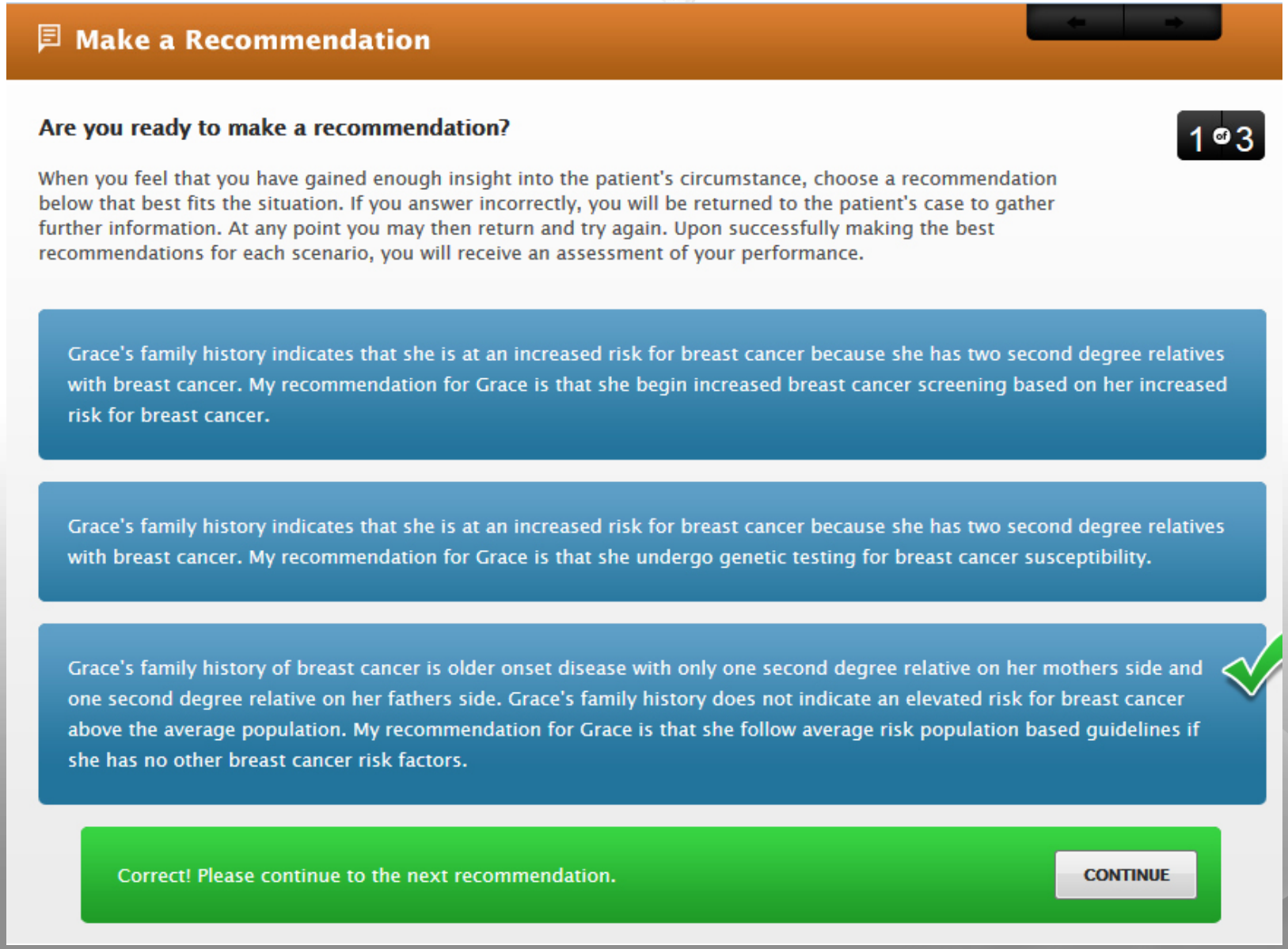
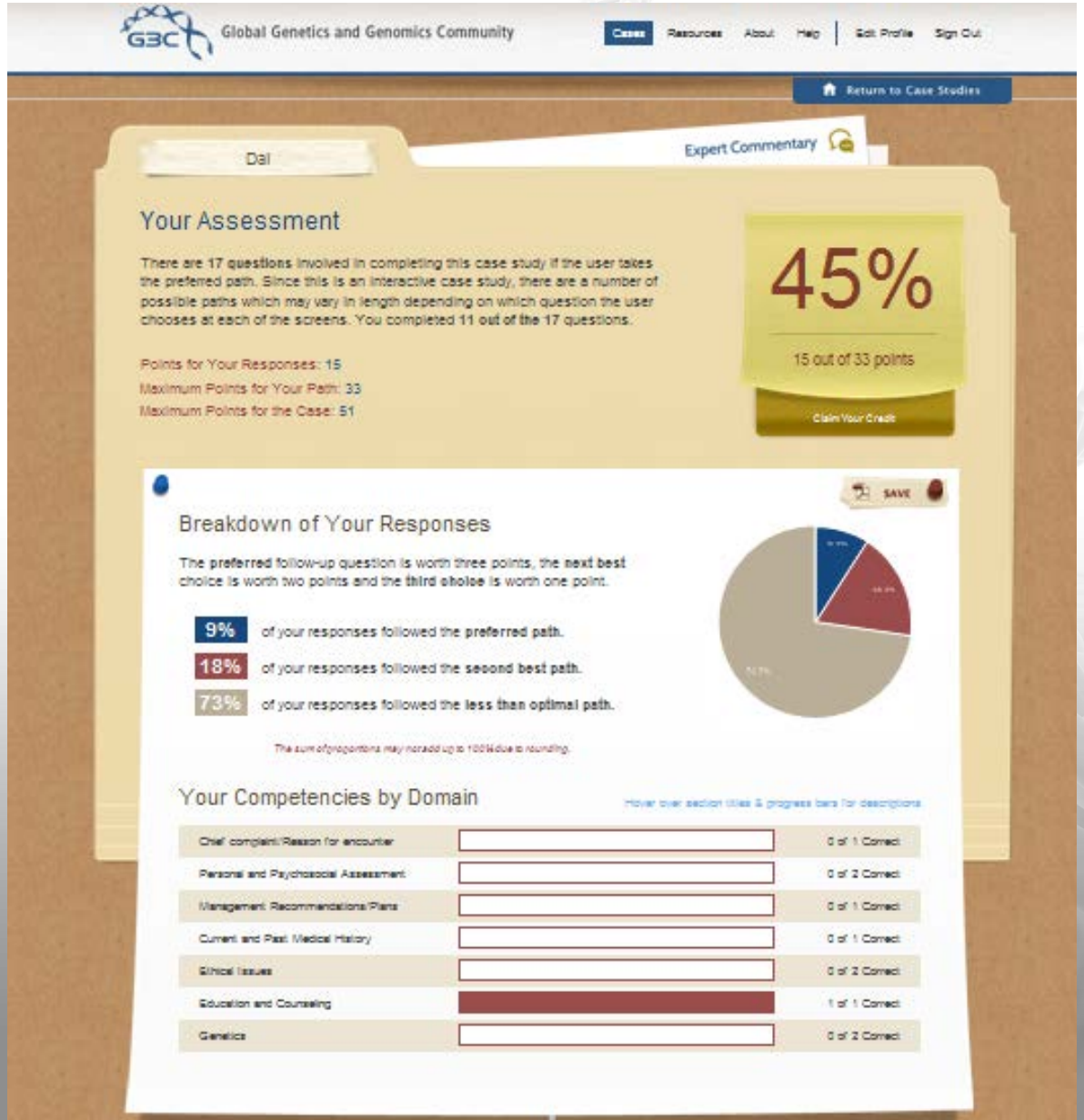
Jeff & Maria
Student Activity
What are the cancer risk management guidelines for men with a BRCA2 mutation?
Resource 1
Resource 2
Resource 3
Resource 4
CC
Jeff: Well, I'm here for my yearly physical. And I completed the ACT for health and the WebHA, and found out that I'm at an increased risk for breast cancer. My dad, incidentally, was found to have the mutation BRCA2, which I was under the impression that could only be passed down by the mother's side of the family.
Maria: But we found out that is not true.
Jeff: Right.
Maria: And really I think the reason we are here today is - for me, it's primarily because I'm concerned about Jeff's health, and I guess I just

Incorporation of Outcome Recommendations



Inclusion of Outcome Assessments



Expert Commentary

About Expert | Ask a question | Closed Caption

Howard McLeod, PharmD

Medical Director, Personalized Medicine Institute

Moffitt Cancer Center

Resources:

Scott, S.A., Sangkuhl, K., Stein, C.M., Hulot, J.S., Mega, J.L., Roden, D.M., Klein, T.E., Sabatine, M.S., Johnson, J.A., Shuldiner, A.R. (2013). Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C19 Genotype and Clopidogrel Therapy: 2013 Update. Clinical pharmacology & Therapeutics, 94, 317-323.
http://www.ncbi.nlm.nih.gov/pubmed/23698643

Adverse Drug Reactions

- Adverse Drug Reactions (ADRs) are defined as any untoward medical occurrence associated with a medication prescribed at the **recommended dose**

Codeine Fatal ADRs

- Deaths have been reported in UMs given codeine for pain management post-tonsillectomy and/or adenoidectomy for obstructive sleep apnea
- 8/15/2012, FDA published a safety communication: Codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death

Ciszkowski, C., et al. (2009). Codeine, ultrarapid-metabolism genotype, and postoperative death. New England Journal of Medicine, 361(8), 827-8.

Kelly LE, et al. (2012). More codeine fatalities after tonsillectomy in North American children. Pediatrics. 129(5):e1343-7

Codeine Fatal ADRs

- 2/20/2013, the FDA updated the safety communication to a new Black Box Warning and Contraindications related to codeine use, noting that codeine is no longer recommended for pain control in children undergoing a tonsillectomy and/or adenoidectomy.

FDA codeine 08/2012 Safety Communication
http://www.fda.gov/Drugs/DrugSafety/ucm313631.htm

FDA codeine 02/2013 Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy
http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm

FDA Drug Safety Podcast: Safety review update of codeine use in children
http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm340524.htm

CPIC Dosing Guidelines

- April 2014 there were updates to the existing CPIC CYP2D6 and codeine dosing guidelines
- The guideline update addresses the current FDA warning of codeine use in children as well as other opioids CYP2D6 metabolizes
- August 2015 the guideline was further updated with a supplemental table providing the association between allelic variants and CYP2D6 enzyme activity)

G3C and Pharmacogenomics

Global Genetics and Genomics Community

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Stephanie — View Patient Info

Name: Stephanie
Age: 25

Background

Stephanie is a 25-year old female who presents to the otolaryngologist to discuss post-tonsillectomy pain management for her youngest daughter, given her older daughter's prior adverse reaction to codeine.

Health Record

Case Notes

Click here to begin

Clopidogrel Pharmacogenomic Phenotype

- Prodrug that works primarily by conversion to its active form in the liver, mediated by the liver enzyme CYP2C19
- Extensive metabolizer (normal) *1/*1
  - normal platelet inhibition
- Intermediate metabolizer *1/*2-*8 or *17/*2-*8
  - Reduced platelet inhibition
  - Increased residual platelet aggregation
  - Increased risk for adverse cardiovascular events

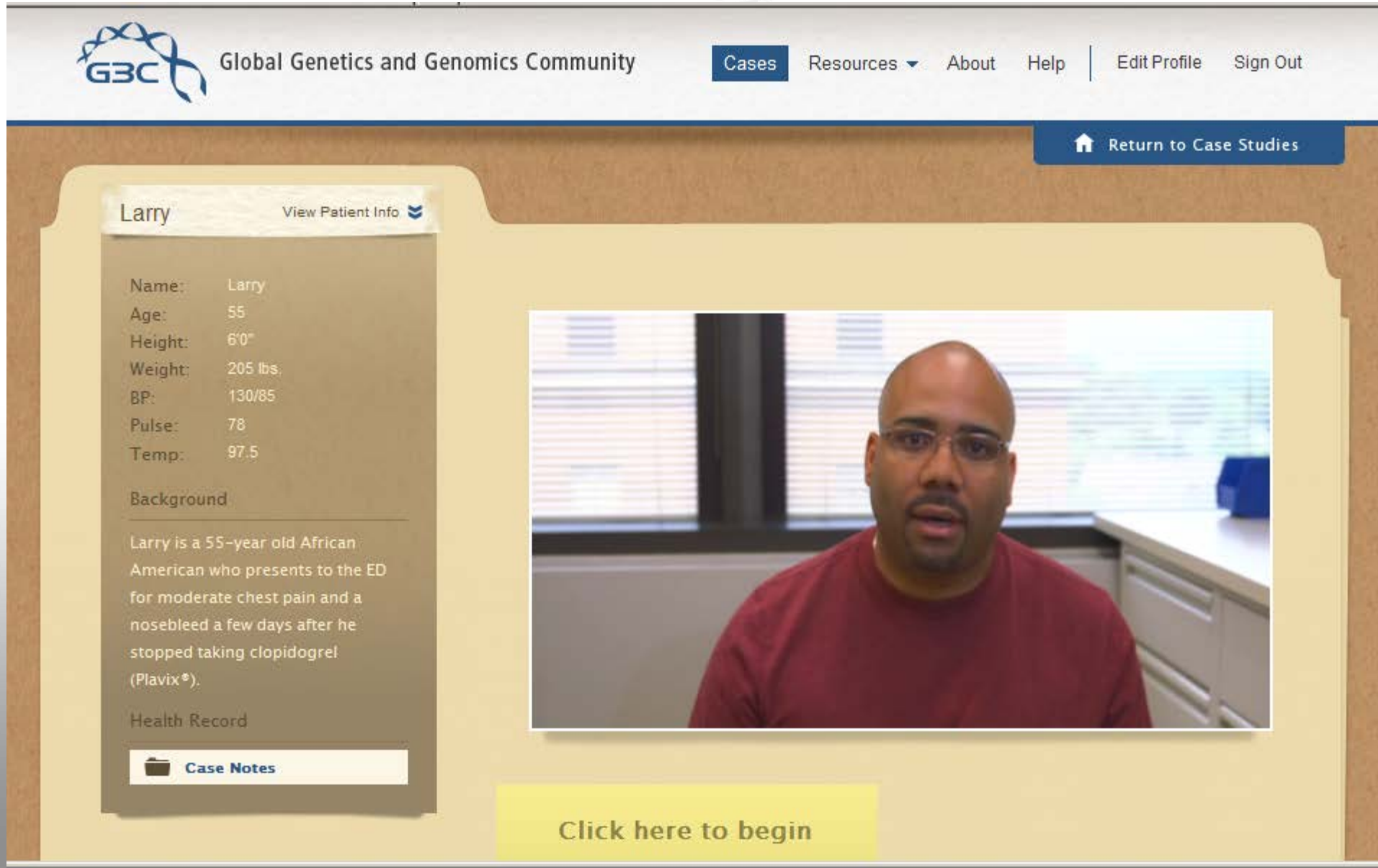
Clopidogrel Pharmacogenomic Phenotype

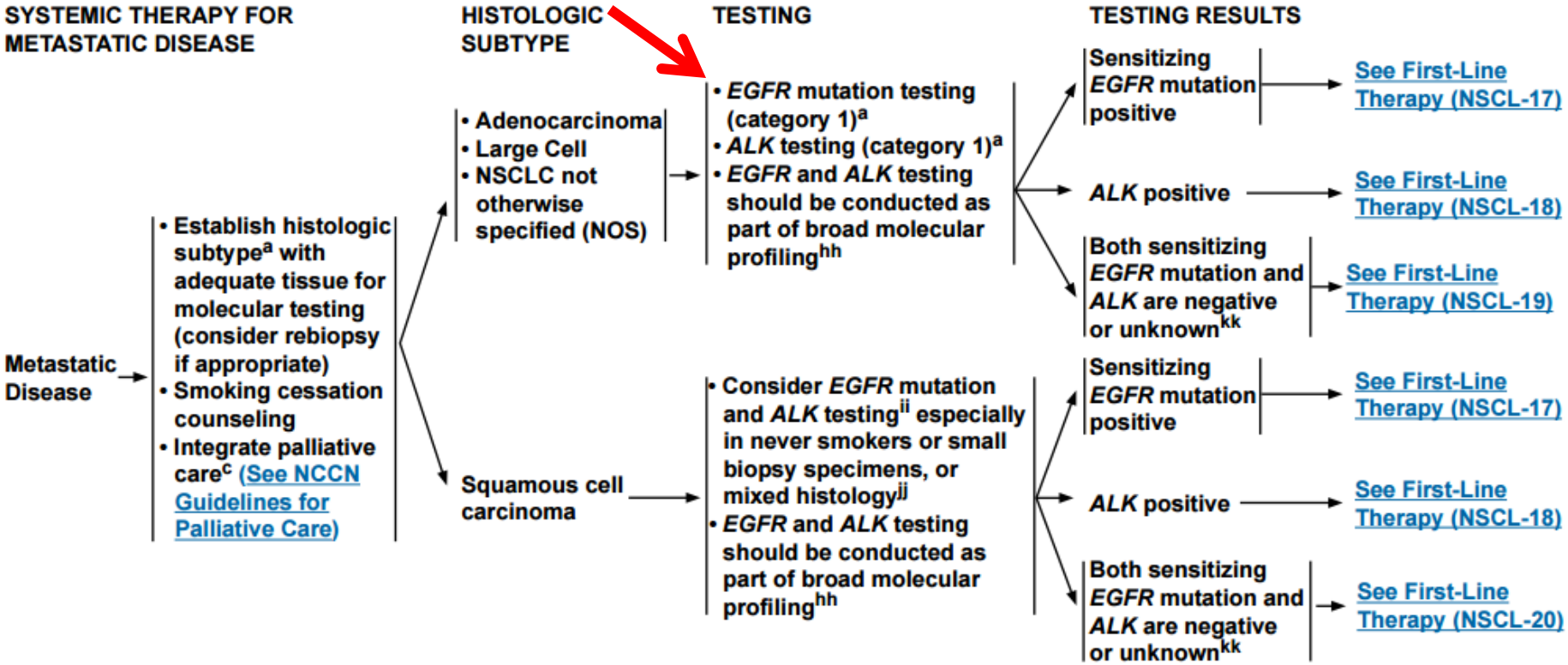
- Poor metabolizer *2/*2-*8
  - Significantly reduced platelet inhibition
  - increased residual platelet aggregation
  - increased risk for adverse cardiovascular events
- Ultrarapid metabolizer *17/*17 and *1/*17
  - Increased platelet inhibition
  - Decreased residual platelet aggregation

CPIC Dosing Guidelines

- In September 2013 there were updates to the existing CPIC CYP2C19 and Clopidogrel dosing guidelines
- The guideline update is more focused on patients with acute coronary syndromes undergoing percutaneous coronary intervention and refined recommendations for variant and novel *CYP2C19* alleles beyond *2
- The full text guidelines and update are provided on PharmGKB as well as a genotype specific dosing guidelines table

G3C and Pharmacogenomics





[a] See Principles of Pathologic Review (NSCL-A).

[c] Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.

[hh] The NCCN NSCLC Guidelines Panel strongly endorses broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).

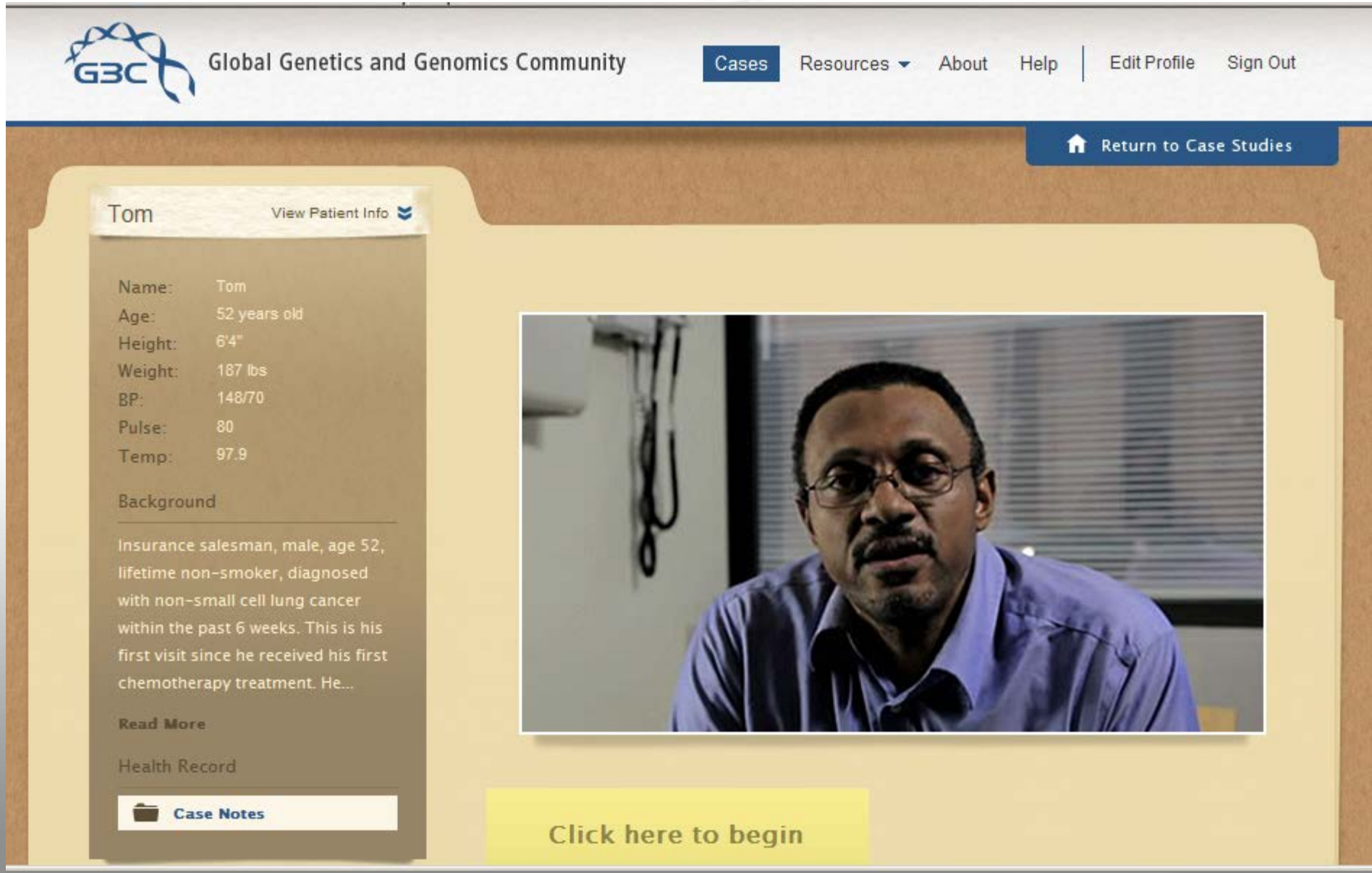
[ii] In patients with squamous cell carcinoma, the observed incidence of *EGFR* mutations is 2.7% with a confidence that the true incidence of mutations is less than 3.6%. This frequency of *EGFR* mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharma G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.

[jj] Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with *EGFR* mutant advanced non-small cell lung cancers with a squamous or squamous-like component. Mol Cancer Ther 2012;11:2535-2540.

[kk] Consider ROS1 testing; if positive, may treat with crizotinib. Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in ROS1-rearranged non-small cell lung cancer. N Engl J Med 2014;371:1963-1971.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

G3C and Pharmacogenomics



Questions/Discussion

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301-435-0538