Future of Prostate Cancer Research/ Addressing Clinical Trials Barriers

Elisabeth I. Heath, MD
Associate Professor of Medicine and Oncology
Wayne State University/Karmanos Cancer Institute
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Most of you realize there are novel advances and treatment options. Most people do not understand a clinical trial: what is the right trial for me, and what are the risks and benefits to me? A clinical trial is a study where people volunteer to test a new drug or a new procedure or a new device. This is how one advances the field: when you do a trial, you ask a question and learn information. You want to show that level of evidence showing this is the right answer. Looking at the levels of evidence, level one means that evidence is obtained from at least one properly designed randomized trial; level two evidence is obtained from different types of trials but perhaps not with such big rigor; level three evidence comes from a respected authority on a particular matter such as prostate cancer. It is important that a patient trust the doctor to know how to tease out evidence; the FDA must be involved.

We now have studies known as phase zero which has no therapeutic benefit. These are altruistic patients who want to contribute to research; that means my patient will take a pill or a drug and you do a one-time biopsy to see if your drug hit the target. Phase zero is not routine, several centers exist in the U.S. including the NCI, but most of us do not do phase zero studies.

Phase 1 studies are done to find out the safety of new drug X. Phase 2 questions whether this treatment works in prostate cancer. Phase 3 looks at whether this agent is better than what is already available. Phase 4, which is post-FDA approval, looks at whether there is a better way to give the therapy.

How do you know what a right trial is? We need criteria such as whether someone is eligible for the trial. Also, the physician-patient partnership is tremendous; if your physician does not endorse the study, the patient is not going to do it because the patient trusts the doctor. There are good resources I give to patients rather than them searching the internet on their own. I refer patients to the unbiased American Cancer Society website, and to Cancer.gov, which is the National Cancer Institute website.

What are the risks and benefits? When I talk, this is what I think as a doctor: you are going to get this, you are going to get new drug, and we are going to see if you are okay, make sure you do not have a fever, and as a patient, you may feel like a guinea pig. This is the disconnect in our thinking between physician and patient. I tell a patient, you are going to be a guinea pig on any study that you do, so let’s just get that clear; once they know that I recognize that, then we can move forward.

The Belmont report outlines how investigators should move forward and protect patients with three mandates. First is recognizing that all people should be respected and have the right to choose what treatments they receive; second is protecting people from harm by maximizing benefits and minimizing risks, or beneficence; and third is trying to ensure that all people share the benefits and burdens of research equally, or justice. It is critical that all three mandates are monitored at each go-round.

Only 3-5% of all cancer patients enroll in clinical trials. This is why it takes 12-14 years to go from Point A to Point B. You cannot move when you have 3% of the population doing anything; you need grassroots efforts to do it. These are the people enrolling: 90% are White; minority, elderly, the rural, the underrepresented, underserved are nowhere to be found. You are making treatment decisions based on people who are not like you, so how is that advancing the field? We are already at a disadvantage.

On ClinicalTrials,gov, there are 1805 trials are currently in play looking at prostate cancer, but none of them specialize in what race or group should be targeting.

What is the risk? Most families fear this: will there be side effects such as death or ability to urinate? The next question that arises is am I going to get a placebo? You do not know which pill you will receive. Patients are worried about confidentiality, and about insurance coverage while on a clinical trial; some coverage does not cover care given unrelated to the clinical trial itself. Another concern is the doctor being too busy to see the patient; it can take an hour to tell a patient and family about a clinical trial. If your family doctor or spiritual leader does not endorse a clinical trial, nor your spouse, chances are you will not go on the study. Our education of patients extends to the people around him, such as family. Sometimes patients fear big bad pharmaceutical companies: how are we supposed to trust that they have our best interest? They just want to make more money. There are Institutional Review Boards, or IRBs, which watch over patients and clinicians, and FDA which watches over all.

Regarding consent forms, which are 30 pages long, everything which can occur on a clinical trial is listed on the consent form, including the possibility of death. There is a time commitment needed for clinical trials, as well as transportation issues. Eligibility excludes certain patients who want to enroll.

Looking at this disparity table in Wayne County, where Detroit is located, there are higher death rates in men with prostate cancer per 100,000; there are higher deaths per incidences in Black versus White. These are numbers in my community; these are numbers facing us day to day. We also have Arab-Americans in our community, the largest such U.S. population in Dearborn, Michigan. Coding of this group is difficult: some want to be called Lebanese, some Egyptian, some Middle Eastern, Middle Eastern American, American Middle Eastern, and they are very specific in the order. Which one do you pick? Self-identification, from all of the data that we are hearing today, is completely inadequate, but even there, they are either coded as Black, non-White, non-White Hispanic, African-American, American-African, you name it. We are trying to determine coding from a genetic standpoint.

We, along with Henry Ford Hospital, have teamed up on a prostate cancer research program; we service the same group of patients. One of the major problems though is literacy. It is important that we improve our understanding of potential genetic variances in cancer biology. If you practice in a high risk population place like Detroit, you know that disease aggressiveness in African-Americans is not the same as in European-Americans. We need better biomarkers beyond PSA and CTCs.

Also, we have to stress that even if you diagnose, it does not mean you are going to die. In fact, if you are diagnosed, you might have a chance to live; this message is not out there. On September 11th, our group will be participating in the 100 Black Men Health Walk in Detroit; these folks are committed to having people live longer, doing cholesterol checks and PSA screens. We need better communication among our participating organizations. Also, it is important to ensure that we have funding: we are often overlooked; we have to say it matters or no one will listen to us. It is important to get everyone, such as Senators and Mayors, involved and engaged; you have to provide evidence based care.

Future of Prostate Cancer Research

- Novel advances in treatment options
  - Sipuleucel-T (Provenge)(Dendreon)
  - Cabazitaxel (Jevtana)(Sanofi-Aventis)
  - Denosumab (Amgen)
  - Abiraterone (Cougar/J and J)
  - MDV3100 (Medivation)
  - TAK700 (Millenium)
- Novel advances in biomarkers
  - CTC (Veridex)
  - PET scans and other imaging modalities

Clinical Trials

- What is a clinical trial?
- Why do we need clinical trials?
- What are the types/phases of clinical trials?
- What clinical trial is right for me?
- What are the risks/benefits?

Clinical Trial

- Studies in which people volunteer to test new drugs or procedures
- Clinical trials tell us what works and what does not work

Why do we need clinical trials?

- Provide evidence of efficacy
  - **Level I:** Evidence obtained from at least one properly designed randomized control trial
  - **Level II:** Evidence obtained from various types of trials (well designed without randomization, case-control
  - **Level III:** Evidence obtained from respected authorities based on clinical experience, descriptive studies, or reports of expert committees
- Food and Drug Administration must approve new drugs and medical devices

What are the types of clinical trials?

- Average time is ***12-14 years*** for a drug to go from pre-clinical laboratory testing to obtaining approval for human use
  - Phase 0: How does the treatment work?
  - Phase I: Is the treatment safe?
  - Phase II: Does the treatment work?
  - Phase III: Is it better than what is already available?
  - Phase IV: Is there a better way to use them?

What clinical trial is right for me?

- Eligibility criteria
- Helps define the question that is being asked in the clinical trial
- Physician and patient partnership
- Websites/resources (www.cancer.org, www.cancer.gov)

What are the risks/benefits?

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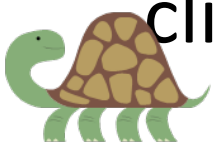
Clinical Trials- Belmont Report

- **Respect for persons:**
  - Recognizing that all people should be respected and have the right to choose what treatments they receive
- **Beneficence:**
  - Protecting people from harm by maximizing benefits and minimizing risks
- **Justice:**
  - Trying to ensure that all people share the benefits and burdens of research equally

Accrual in Clinical Trials

- **3-5%** of adults with cancer enroll in clinical trials
- 90% of patients enrolled are white
  - Minority
  - Elderly
  - Rural
  - Underserved
- 1805 clinical trials in prostate cancer in clinicaltrials.gov



http://www.cancer.gov/ncicancerbulletin/051810/page7

Barriers to Accrual

- Concern about risk (benefit>risk)
- Concern about placebo
- Concern about medical information confidentiality
- Concern regarding insurance coverage
- Appropriate clinical trial not mentioned/not available
- Physician/family/spiritual leader endorsement

Comis RL. J Clin Oncol 2003, 21; 765-6.

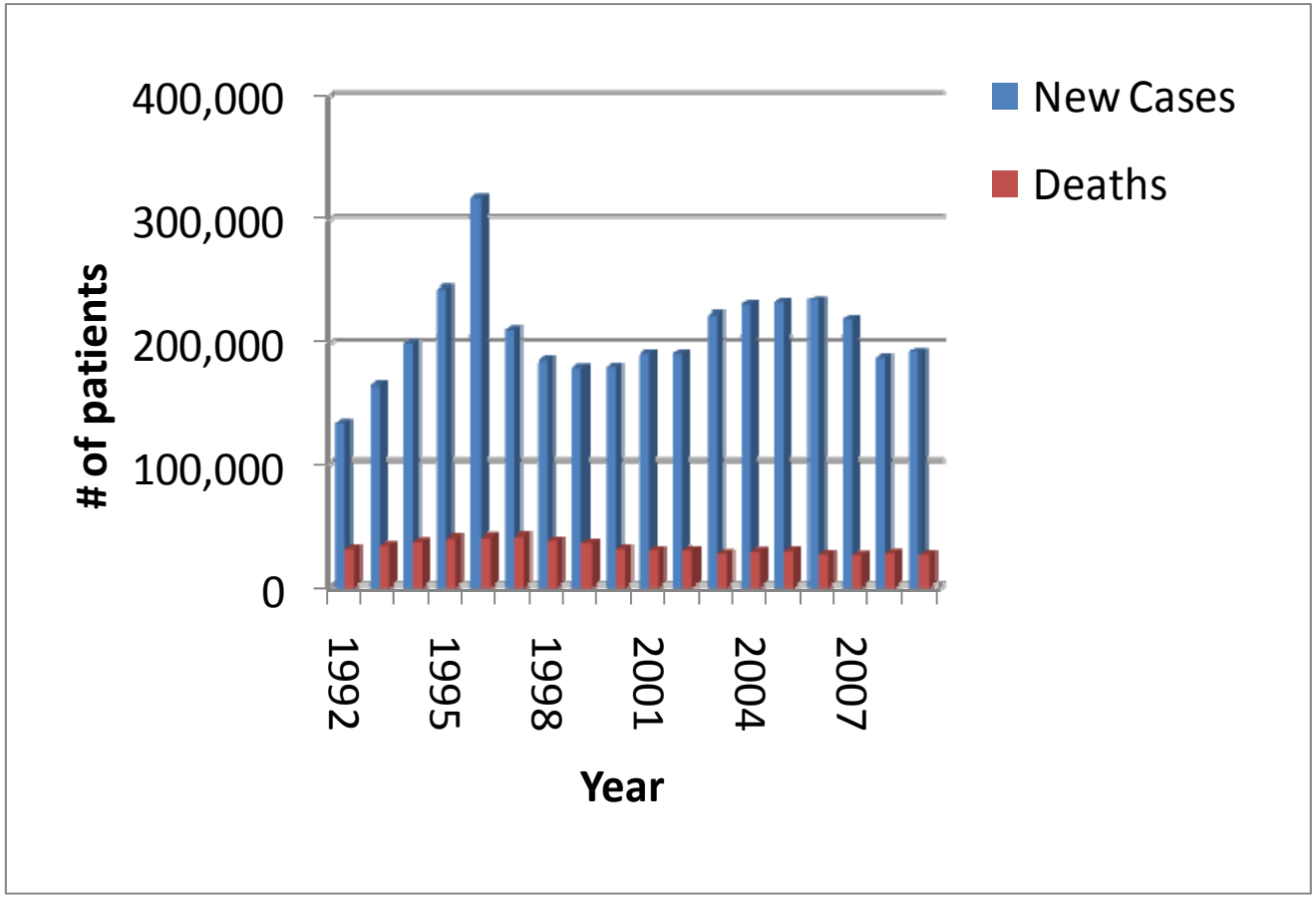
Barriers to Accrual

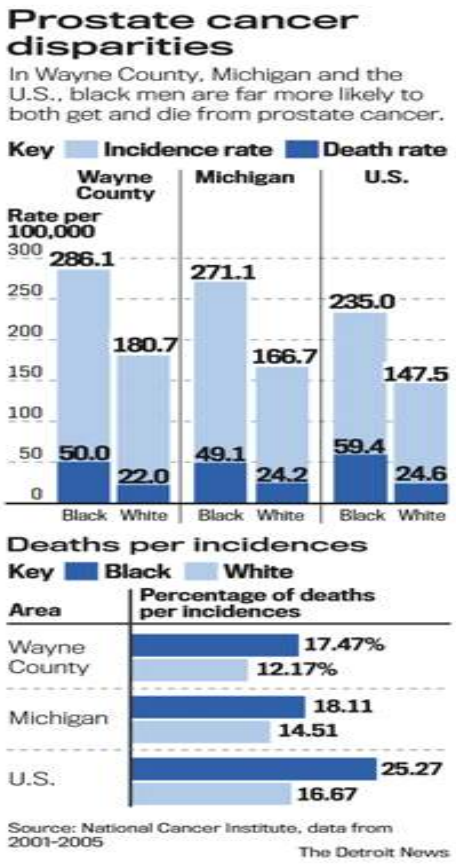
- Mistrust and fear of medical research
- Mistrust and fear of pharmaceutical sponsor
- Difficult consent form (8th grade reading level)
- Time commitment
  - Grandparents as parents
- Transportation issues
- Condition did not meet eligibility of study

Recruitment of Minority Populations at Wayne State University, Detroit, MI

- Recognize and identify the problem
- Prospectively and proactively provide solutions
- Recognize barriers to accrual to clinical trials are higher with regards to recruitment of minority populations

Prostate Cancer Disparities





Recruitment of Minority Populations at KCC

- Prospectively and proactively provide solutions
  - Prostate Cancer Specific Database tracks African-American, Middle-Eastern, Hispanic, Asian/Pacific Islander, White (non-Hispanic)
  - Oncore clinical trials database
  - Standard Operating Procedures on how to collect information (patient self-identification)

Recruitment of Minority Populations at KCC

- Recognize and identify the problem
  - Detroit and Southeastern Michigan is comprised of many ethnic/racial groups
  - Large African-American and Arab-American population
  - KCC evaluates and treats approximately 6,000 new patients

Recruitment of Minority Populations at KCC

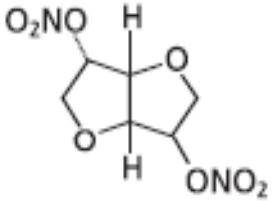
- Recognize barriers to accrual to clinical trials are higher with regards to recruitment of minority populations
  - Consent form; literacy issues, translation issues, reading level
  - Functional illiteracy rate in Michigan is 18%
  - **Functional illiteracy rate in Detroit is 47%**
  - Detroit Unemployment rate 10.3%

Why is Recruitment of Minority Populations Important?

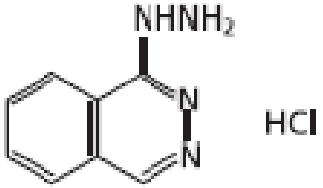
- Appropriateness of medical recommendation
- Improvement in our understanding of potential genetic variances in cancer biology and disease aggressiveness
- Under-funding of treatment of disease disproportionately high in minority populations

Why is Recruitment of Minority Populations Important?

- Appropriateness of medical recommendation
  - Approval of BiDil (Isosorbide dinitrate/hydralazine
    lrochloride) in *African American* patients with
    ıgestive heart failure



  - FDA approved 2005



A-HeFT Trial

- BiDil versus placebo
- 1050 self identified black patients
- LVEF < 35%
- Planned trial of 18 mos
- Terminated early at 12 mos

Figure 1: Kaplan-Meier Plot of Time to Death by All Cause in Black Patients (A-HeFT)

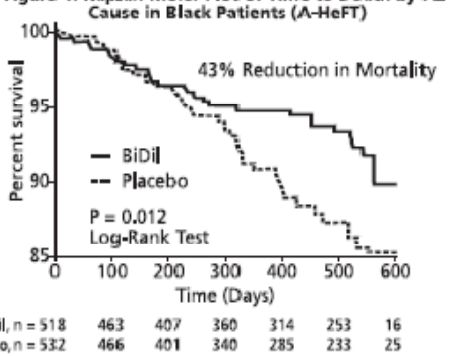
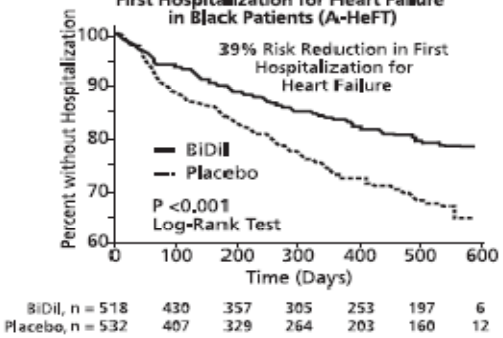


Figure 2: Kaplan-Meier Plot of Time to First Hospitalization for Heart Failure in Black Patients (A-HeFT)



Taylor AL et al. NEJM 351; 2049-57. 2004.

Why is Recruitment of Minority Populations Important?

- Improvement in our understanding of potential genetic variances in cancer biology and disease aggressiveness
  - Reduce health disparity
    - Need for more biomarkers
  - Increase efforts in appropriate screening and prevention
    - Diagnosis does not equal death
  - Increase efforts in treatment advances

Prostate Cancer Nomogram

- Utilization of PSA, clinical stage, and Gleason score to predict the pathologic stage at time of surgery (Partin Tables)
- Evaluation of 5,730 males; 89% Caucasian, 7% African American, 4% other
- Unknown role of nomogram in minority population

Prostate Cancer Nomogram

- Evaluate race/ethnicity on the accuracy of the nomogram for predicting pathologic stage
- Combined databases from WSU/KCI, Henry Ford Hospital, VA SEARCH, University of Texas Health Science Center
- Race is not a factor for predicting pathologic stage

Heath EI et al. Urology 71; 51-55, 2008.

Why is Recruitment of Minority Populations Important?

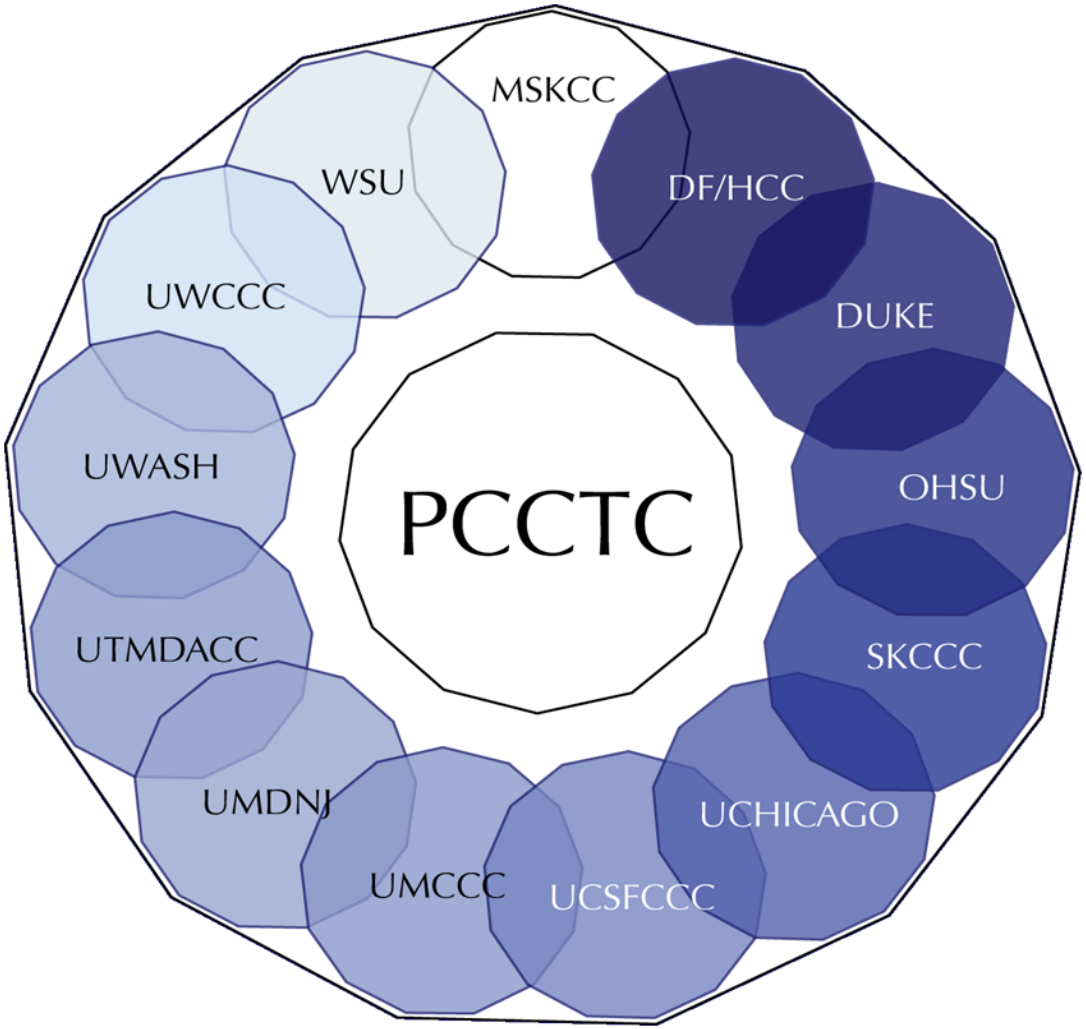
- Under-funding of treatment of disease disproportionately high in minority populations
  - Centers for Population Health and Health Disparities (WSU one of 8 sites)
  - Provide opportunities to study biological, behavioral, psychological, cultural and social precursors of disease

Why is Recruitment of Minority Populations Important?

- Under-funding of treatment of disease disproportionately high in minority populations
  - Emphasize need for increasing funding to comparable levels for other populations
  - Provide evidence-based medical care in minority populations

The Prostate Cancer Clinical Trials Consortium

Our mission is to design, implement, and complete hypothesis-driven phase I and II trials of novel agents and combinations that could prolong the lives of patients with prostate cancer.



DOD W81XWH-08-PCRP-CCA; Heath EI, PI, WSU # PC081656

Patient Advocacy

- Strong advocacy groups helping to educate patients and families about clinical trials
  - Prostate Net
- Increasing public awareness through written and television media
- Increasing local and national meetings focused on racial disparity and prostate cancer

How to Increase Enrollment

- Increasing awareness of active foundation groups such as Prostate Cancer Foundation, American Society of Clinical Oncology
- Community engagement
- Patient navigators
- Recognition of team effort
  - Patient, family, primary care physician, oncologist, urologist, nurse, social work, community leaders, spiritual leaders

Ask About Clinical Trials

- Ask your doctor
  - List of questions www.cancer.gov/clinicaltrials
  - Bring a family member or friend
  - Ask why you don’t qualify for a clinical trial
- Take your time
- No pressure

Conclusions

- Clinical trials are critical in advancing medicine
- Barriers to clinical trials are encountered by all patients, especially in the minority population
- Special efforts must be placed to help increase enrollment to clinical trials

Conclusions

- Provide appropriate medical recommendations
- Improve our understanding of potential genetic variances in cancer biology and disease aggressiveness
- Increase grant/research funding in diseases that disproportionately effect minority populations

Websites

- www.karmanos.org
- www.cancer.gov
- www.cancer.org
- www.prostatecancerfoundation.org
- www.prostatenet.org