

Harmonizing Research Goals with Meeting Clinical Needs: Patient perspectives on clinical trial design

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Independent work; based primarily from direct 10-year
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“You can see a lot just by looking.” ~ Yogi Berra

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Patient advocates are people closely touched by a disease. We interact with the patient community in order to discover and understand needs.

We communicate about obstacles and opportunities; and about the human costs ... trying to keep the urgency alive, which can many times be lost when you look at a disease in the abstract.

In memory of

Rick Stimmel, Denise Stafford, and Dan Stevens



Rick Stimmel

Just 50 years old,
caretaker for his elderly
mother, died from severe
sepsis, a complication of
the toxic side effects of
chemotherapy

Dx: 7/00; Deceased: 2/05



Denise Stafford

Just 51 years old
Dx: 10/03;
Deceased: 3/06
6 R-CHOP + 2 R-CVP
- PR

9/04 4 x R - PR

10/04 RICE x 3

1/05 ESHAP x 2

6/05 Fludara + R +
Doxil

7/05 2nd treatment -
continued improvement

8/05 3rd treatment -
3rd time the charm?



Dan Stephens

Just 44 years old; leaves
behind a wife and infant son.
He passed away when
aggressive treatment failed to
stop high-risk disease.

Dx: 12/02; Deceased: 3/05

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I'm dedicating this talk to the memory of Rick Stimmel, Denise Stafford, and Dan Stephens, lymphoma patients, and valued colleagues, who recently passed away.

Rick and Dan both added to our knowledge by participating in clinical trials.

Each provided generous support and encouragement to other patients. Their unexpected deaths saddened us; ... each passing a very personal reminder to all in our group of the danger we face.

We need each other

- **Importance of timely participation** – delays are costly to sponsors and to patients.



If patients fail to sign on in adequate numbers ...

... the **assessment of the therapy** will not be made no matter how well the study is designed from the point of view of regulators and scientists.

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I believe it's evident that we need each other, and that we need to communicate better.

Delays in trial enrollment are costly to drug sponsors, and to patients. Indeed, the urgency of our situation requires that the drug discovery and evaluation system become as efficient as it can be.

I think it's well-accepted by the industry that patient enrollment is **THE** issue, because without it the assessment of the protocol will not be made no matter how well it's designed from the point of view of regulators and investigators.

Patients' perspectives

Urgency the scope of the disease, aspects of treatment toxicity

Crisis in clinical research

Proposals

how we might do more efficient and ethical clinical research

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I have 3 main objectives today:

The first is to describe the urgency: the need for more effective cancer therapies; and to give patient perspectives on aspects of treatment toxicity ... in both the clinical and research settings.

The second is to provide comment on the crisis in clinical research: the stagnation described in the FDA report on The Critical Path; the failures of preclinical models to predict the toxicities and efficacy of new agents; and the very low enrollment rate of patients in clinical trials

Finally, I'll make the case for a more patient-centered approach to doing clinical research.

URGENCY

The scope and impact of the diseases called cancer
Aspects of treatment toxicity

*"Not everything that counts can be counted;
not everything that can be counted counts."*

~ Albert Einstein

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In this section I'll try to convey the urgency:

**The scope and impact of the diseases called cancer ...
and the many aspects of treatment toxicities.**

Urgency: every family

Cancer will affect virtually **every family**

Lifetime risk:

1 in 2 men

1 in 3 women *

* SEER 2002



560,000 new cases this year

Reply to patients who severely mistrust the system: *“Regulators, doctors, drug developers, and scientists also get cancer ... and their children, parents, spouses, and loved ones. We are in this together. There is no conspiracy.”* ~ Len Rosen

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The data tells us that cancer is everyone’s problem.

As difficult as it may be to realize, ... or want to: 1 in 2 men will get a serious cancer, and 1 in 3 women.

That is to say: we are all future patients or caregivers – and that it’s in everyone’s best interest to make clinical research as efficient as it can be.

I’ll note that there are many people with cancer who severely mistrust the medical system; Who will avoid or delay even proven medical treatment, while trying unproven alternatives.

This is another aspect of cancer drug toxicities. But everyone gets cancer, including regulators, doctors, drug developers ... and their loved ones ... And while the system is not perfect, we counsel the patient community that there is no conspiracy -- and to make decisions that are evidence-based.

Aspects of toxicity ...

- **Can contribute to death**
 - Bone marrow toxicity and subsequent infection is a leading cause of death in lymphoma patients. ^{1,2}
- **Can limit future treatment choices**

1. *Ten-year survey of incidence of infection as a cause of death in hematologic malignancies: study of 90 autopsied cases. Acta Haematol. 1995;93(1):25-30. [PMID: 7725846](#)*
2. *Causes of death in children diagnosed with non-Hodgkin's lymphoma between 1974 and 1985. Arch Dis Child. 1992 Nov;67(11):1378-83. [PMID: 1471892](#) | [Related articles](#)*

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Starting here, I'll cover important aspects of treatment toxicities, which could help to inform or guide the direction of clinical research and trial design. ...

There are two aspects of toxicity that are well-known to cancer patients:

- 1) that the side effects of treatment can contribute to your death;
- 2) and also narrow your range of future treatment options.

In fact, for lymphomas, bone marrow toxicity, leading to infection, might be the leading cause of death ... and for indolent lymphomas it seems that we don't run out of options so much, as the ability to tolerate them.

Toxicity leading to “a narrowing range of choices”

...

*“In a sense Billy's no longer at the helm,
the conditions are,
and all he can do is react.*

*If danger can be seen in terms of a
narrowing range of choices, Billy Tyne's
choices have just ratcheted down a notch.”*

~ The Perfect Storm.



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In the “Perfect Storm” the narrator defines DANGER as a narrowing range of choices; in the clinic, patients and physicians call it “burning bridges.”

When designing clinical trials investigators and sponsors should be mindful of this aspect of a study protocol, for it can have a significant impact on enrollment.

Unproductive Toxicity ...

a function of:

Not **matching the drug to the patient.**

...when a drug has a 20% response rate,
80% suffer toxicity for no benefit.

Not **accounting for patient differences**

in the biology of the tumor

in immunity

in metabolism, half-life ...

"The trick with molecular targeting is that you have to be able to match the drug to the patients. And until you understand how the drugs work, why they work, and for whom they work, your results might not be as remarkable as you would like for them to be.

Once we understand how to match the drug to the patient, I think we will see many, many examples like imatinib [Gleevec]." ~ Dr. Brian Druker, Howard Hughes Medical Institute

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Obviously, toxicity is bad, but what can be worse than unproductive toxicity – getting only the side effects of the drug, and no benefit ... and often significant harm?

Unfortunately, for some cancers this risk is common, and considered better than having no chance at all. It appears that unproductive toxicity is a function of not accounting for patient differences:

in the biology or microenvironment of the tumor

or in immunity,

or in how the drug is metabolized. ...

It was this quote from Dr. Druker, about matching drugs to patients that got many advocates thinking about the necessity for a new approach to clinical research.

... the trial and error aspect of care

The ongoing uncertainty;
the risk of unproductive toxicity

“While I'm grateful for the number of options we have before us, sometimes I wish we didn't have quite so much to analyze and contemplate (and wonder if we got wrong).

Ironic that, at the end of the day, it's still a crap shoot. ”

~ Mark F. (Lymphoma survivor)

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Mark, a member of our lymphoma support list, writes:

“While I'm grateful for the number of options we have before us, sometimes I wish we didn't have quite so much to analyze and contemplate (and wonder if we got wrong).”

His words speak to the uncertainty and anxiety: the trial and error aspect of care; the concerns about unproductive toxicities.

Patient differences and unpredictable toxicity

- Vincristine pharmacokinetics: ... “*although significantly influenced by diagnosis, largely remains unpredictable.*” ¹
- “*Clearance can vary from **23 to 85 hrs** for adults; and from **10 to 40 hrs** in children.*” ²

1. Vincristine pharmacokinetics after repetitive dosing in children.; Gidding CE, Meeuwse-de Boer GJ, Koopmans P, Uges DR, Kamps WA, de Graaf SS. [PMID](#) Cancer Chemother Pharmacol. 1999;44(3):203-9.
2. becancer.bc.ca

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Here is yet another aspect of treatment toxicity: that it can be unpredictable, which also relates to patient differences.

I know that some patients treated for lymphoma can suffer painful and irreversible neuropathy, because of how slowly their body clears Vincristine.

Note that the clearance of this drug can vary significantly in children and adults.

My impression is that dose and scheduling adjustments of this drug is still guided by patient reporting of symptoms.

CRISIS

in clinical research

* "We are in the midst of a clinical research crisis in the USA. Very few patients, less than 5% of all available patients, enroll in protocol studies." ¹

¹ The ODAC Chronicles 2005 ~ Antonio J. Grillo-Lopez, MD Chairman, Neoplastic and Autoimmune Diseases Research Institute

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The next section of the talk is about the “clinical research crisis.”

But also, it’s about opportunities for accelerated progress and innovation, if we dare to change the approach.

Evidence of the crisis

What's Wrong with Our Cancer Models?

“Response rates among unselected cancer patients in phase I studies are seldom more than 10%.”¹

“Nine of ten attempts to bring a cancer drug to market fail.”¹

“Very few patients, less than 5% of all available patients, enroll in protocol studies.”²

1. **What's wrong with our cancer models?**
Alexander Kamb, Novartis Inst. For Bio. Med.
2. **The ODAC Chronicles 2005 ~ Antonio J. Grillo-Lopez, MD Chairman, Neoplastic and Autoimmune Diseases Research Institute**

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On this slide is evidence of the clinical research crisis cited by Alexander Kamb and Dr. Grillo Lopez. ...

Given the low response rates in phase I studies shown here, (less than 10%) ...

and that one in ten attempts to bring a cancer drug to market succeed, ...

we might conclude that the low enrollment in clinical trials indicates good judgment by patients and their treating physicians.

Poverty of riches



ClinicalTrials.gov
A service of the U.S. National Institutes of Health

[Home](#) | [Search](#)

Search results for lymphoma [CONDITION] are shown

Include trials that are no longer recruiting patients.

681 studies were found. Here are studies 1 to 50.

1. Recruiting [Chemoradiotherapy and Perio](#)
Conditions: Adult Burkitt's Lym

The number of new agents

The limited patient pool

"it was the best of times, it was the worst of times"

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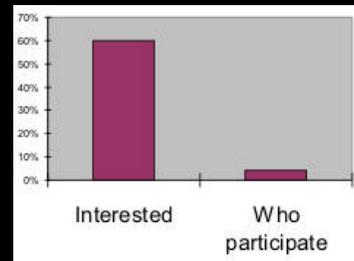
It's clear to me (for lymphomas at least), that the gap between what is and what's possible in respect to effective use of treatments has never been wider. ...

To close the gap we need to test new agents and protocols, but the sheer number of studies is an obstacle to progress, as each must compete for patients in the same small pool - approximately only 5% of the patient population.

Clinical Trials: Interest versus Participation

- Patients recently rated clinical trials information as the most important Internet service, with **60% of patients actively seeking access to clinical trials**

... But **fewer than 5% of cancer patients actually participate** in clinical trials. ¹



¹ CancerConsultants.com™ - Internet Interest in trials.

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Here we have the results of a survey conducted by CancerConsultants.com. ... It found that 60% of patients (who use the Internet) are actively seeking access to clinical trials, but less than 5% participated, overall. ...

These results suggest that the primary problem with accrual is not the attitudes of patients. ...

I might add that our own online survey is showing a similar % of patients so far – about 65% have considered clinical trials to treat lymphoma.

Crisis: Patient Enrollment

- “Understanding Cancer Patients’ Needs”
- Lack of resources
- Health insurance restrictions
- Confusion about research and medical care, and study procedures ... which study? 1
- Excessive or undesirable tests:
 - Bone marrow biopsies
 - Exposure to excessive amounts of imaging radiation
- Need to involve community oncologists?
- Disqualifications, restrictive protocols

(1) Understanding Cancer Patients’ Needs, Concerns is Key to Improving Clinical Trial Participation. - UC Davis Cancer Center study

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This slide shows some well-known barriers to patient enrollment in clinical trials. Limited patient resources, for example, that can make travel to a study site impossible. Health insurance restrictions, or the belief that these restrictions are present.

Confusion about research procedures. Patient confusion about the goals of research. Excessive or undesirable tests, such as multiple bone marrow biopsies, and frequent CT scans. And expectations that they are likely to be disqualified by one entry criteria or another.

In my view, the authors of the UC Davis study had it right in choosing the title of the report shown here. That is, that understanding cancer patients’ needs is the key to improving clinical trial participation ... and these needs can be quite variable depending on the cancer and the clinical circumstances.

FDA on the promise of *innovation*; the evidence of *stagnation*

“... the current medical product development path is becoming increasingly challenging, inefficient, and costly.

... the number of **new drug and biologic applications** submitted to FDA has declined significantly.

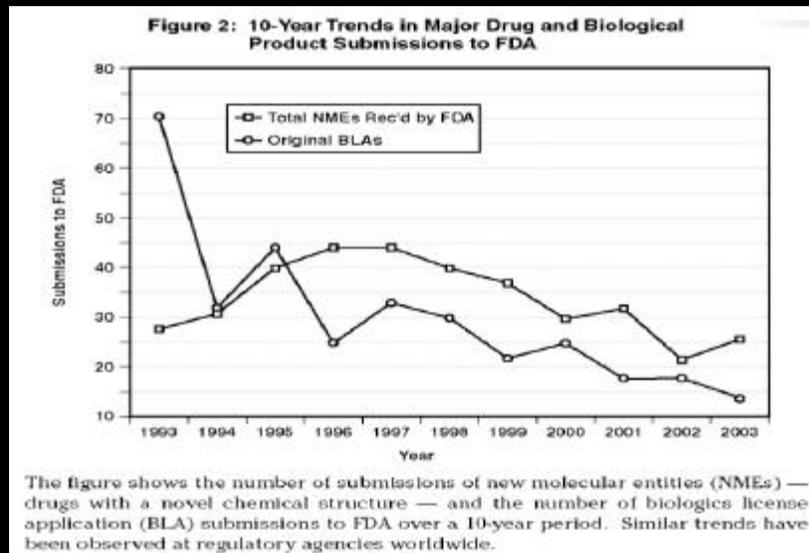
... If the costs and difficulties of medical product development continue to grow, innovation will continue to stagnate or decline, and the biomedical revolution may not deliver on its promise of better health.”

1. *Innovation / Stagnation – Challenge and Opportunity on the Critical Path to New Medical Products – FDA (2004)*

Here we have a startling assessment from the FDA in the publication referred to as the Critical Path.

I can tell you that this text – coming from this source - is particularly frightening to people who face cancers ... or should be.

Evidence of stagnation – a slide



1. *Innovation / Stagnation – Challenge and Opportunity on the Critical Path to New Medical Products ~ FDA (2004)*

And here, despite the promise for innovation by new technologies, we see pictured: a significant 10-year downward trend in major drug submissions to the FDA, ... reported by the FDA.

Cancer Phase I Response Rates

Are we discarding potentially effective drugs?

Tumor type	Response R ¹	Prevalence ²	Potential *
Colorectal	2/476 (0.4%)	1,051,682	4,206
Lung	10/196 (5.1%)	350,679	17,884
Kidney	6/147 (4.1%)	221,270	9,072
Breast	5/94 (5.3%)	2,290,049	121,372
Prostate	4/88 (2.3%)	1,831,929	42,134
NHL **	~ 10% ?	347,039	34,703

* Potential of benefit is calculated as Prevalence * Response Rate.

** Response rates for NHL were not provided, but this disease is typically sensitive to treatment. The 10% is a lay conservative estimate.

1. Alexander Kamb What's wrong with cancer models – trials conducted between 1999 and 2002
2. SEER - 2002

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This table shows response rates for cancer drugs in phase I trials.

My take is that differences in clinical responses among participants means that there's an underlying differences in the disease, or in the patients.

But if we can identify who the drug is for, there's a potential to benefit many individuals. For example: a 2% response in 1.8 million patients with prostate cancer is 42,000 individuals, in the US alone.

Note: that when we develop targeted drugs for molecular subtypes of the disease, orphan drug incentives may well apply. And targeted drugs may be effective across multiple cell types.

Discussion on FDA spokesperson remark: "We [at the FDA] do not want to be a roadblock, but if we don't have the tools to know who can benefit from a drug, we will not be able to approve new drugs," says Dr. Woodcock

PROPOSALS

for doing efficient clinical research

Harmonize research goals with meeting the clinical needs of study participants
Augment competition with cooperative efforts: shared resources, data, and tools

*“When a task is difficult you have to change the approach;
you have to create and apply new tools.”*

~ Charles Schwartz (my father)

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The final section is about the need to change the approach to clinical research. Proposals from the patient community.

Study design: Harmonize Research Goals with Meeting Clinical Needs

There is often a tension between research goals and optimally meeting clinical needs of patients.

How to make progress?

- **Clinical trials that provide answers ... How else?**

... Dependent on good study design and **patient participation ...**

... Dependent on **study protocols that are attractive as treatment decisions**

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To have confidence in the drugs we use, we ought not lower standards for testing, a remedy proposed by some spokespersons in the industry, and in the patient community as well. ...

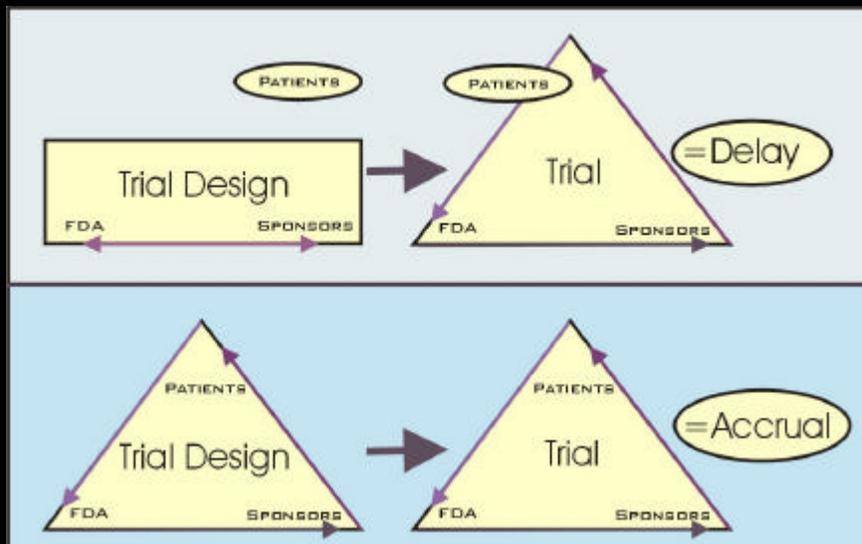
... But we have to address the enrollment problem in clinical trials - ask why, and make changes accordingly.

I think it's vital that we make clinical trials more desirable or reasonable as treatment decisions. It won't be easy, because as you know there's often a tension between getting research answers, and optimally meeting the clinical needs of the participants.

However, it may be that more efficient enrollment can offset many problems; ... and trials that select patients based on biological characteristics of the tumors targeted by the investigational agents, will likely be more attractive to patients.

And if response rates in stratified studies increase as expected, fewer participants may be needed to obtain definitive answers: Reducing time, expense, and most importantly, the danger to the participants. ... *We already see a recent example of this: Revlimid for a molecular subtype of MDS recommended by ODAC for approval based on phase II data.*

Patient Input on Trial Design ...



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This slide simply illustrates the logic of involving patient consultants early in the design of clinical trials. Above patients are shown outside the decision and planning loop. ...

We believe that including the primary stakeholders in the clinical trial design process is bound to result in fewer surprises and faster accrual.

Patient Input on Trial Design

Locating Qualified Patient Consultants?

- Non-profits, FDA
- Locate individuals who:
 - Understand the disease
 - Have the disease and experience the treatments
 - Face the choices
 - Recognize purpose & requirements of clinical studies – the importance of answering study questions.
- Confidentiality agreements

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Qualified consultants have and understand the disease, face the choices, and also recognize the purpose of clinical studies. Scientists with the condition, for example.

Probably the best way to locate qualified individuals is to contact one of the many non-profit organizations. To safeguard intellectual property, you can require that consultants sign confidentiality agreements.

The FDA is beginning to provide patient consultants to participate in End of Phase II meetings, and patients are represented in ODAC (Oncology Drugs Advisory Committee) meetings as well.

Participation: Emerging Tests

May increase patients' confidence/incentives

- Increasing confidence:
 - DNA typing and biomarkers that may predict:
 - Response to the investigational agent or the pretreatment – **avoiding unproductive toxicity; match drug to patient.**
- Increasing patient incentives to participate:
 - Tests that may help predict:
 - The clinical course of the disease, or
 - Likely response to standard treatments.

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High quality information is the basis for good decision making. To make progress we need to better characterize the disease and the patients, which provides the context and explanation of the outcomes.

I believe the use of emerging tests in clinical trials, such as molecular profiling, can help to make clinical trials more attractive to patients than standard medicine.

Participation: Features of Desirable Studies

- Potential to:
 - ✍ **Cure** – particularly if risk is equivalent to standard approaches when standard therapies are not curative.
 - ✍ Increase duration of response, without adding toxicity – without precluding future options
 - ✍ Stabilize with minimal toxicity
 - ✍ Improve quality of life
- And for management approaches:
 - Use **least toxic agents first**.
 - Have low risk of **unproductive toxicity**
 - Are unlikely to **burn treatment bridges** . . .



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It's very difficult to generalize, but these are some characteristics that patients are looking for in trials (for lymphoma at least).

The potential to cure is number one, of course, especially when standard therapies do not, ... but the risk must be considered equivalent to standard approaches.

Patients may be more likely to try new therapies to manage disease that appear safer than standard approaches.

In general, cancer patients are risk averse, and will avoid protocols that appear to limit future treatment options: They want to keep their options open, particularly when the goal of treatment is disease management.

Note: We are beginning to survey the lymphoma patient community to verify or test these impressions.

Endpoints: Proving Survival Benefit for Indolent Cancers?

- Impractical to prove for indolent cancers.
- Precludes use of crossover companion studies.

FDA on drugs with favorable toxicity profiles:

“47% of regular oncology drug approvals had response rate or time to tumor progression as the primary or co-primary end point in trials supporting approval.” ...

... given the favorable toxicity profiles associated with hormonal drugs compared to conventional cytotoxic agents, **RR and TTP are considered adequate surrogates for a better life.**”

See Endpoints and US FDA Approval of Oncology Drugs, April 2003

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As you know, proving a protocol provides a survival advantage is an important research objective, but this endpoint can reduce study flexibility. For example, the survival endpoint can preclude participants from crossing over to the investigational arm of a randomized study on treatment failure.

For indolent cancers, survival is not an ideal endpoint for proving clinical benefit. Assessments will be confounded by patient access to numerous treatments on relapse - including investigational treatments. ...

The good news is that the FDA seems to agree that drugs having a favorable toxicity profile may win approval by other means, as shown here.

Potential Advantages of Adaptive Design to Patients

- Making study protocols less dangerous
- Increasing the odds of benefiting in a study
...steering participants or modifying protocols to make them safer/better based on real-time results
- Reducing unproductive toxicity ...
ending less promising protocols faster.

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On this slide is a list of the possible advantages of adaptive design to the participants in clinical trials.

In short, the flexibility of adaptive design can improve the risk/benefit profile of clinical trial participation, making it less dangerous and more likely to result in clinical benefit.

Future patients also benefit from more efficient study design – all of us.

Utility of adaptive design?

- *Time-dependent endpoints?*
- *Indolent cancers?*
- *Biomarkers?*

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Perhaps the utility of adaptive design will depend on whether the cancer is indolent or aggressive, ...

... if the chosen endpoint can be achieved quickly, such as tumor reduction, ...

... or requires long periods of time: to measure time to progression and overall survival?

It seems that the use of validated biomarkers will be essential to the broadest use of adaptive design.

Is this Adaptive Design?

- Can protocols **adapt to differences in the patient and the disease?**
 - Immune competence and characteristics, polymorphisms?
 - Clinically unique disease & response to treatment
 - Select patients based on underlying biology of the tumor, and microenvironment; not just the cell of origin?

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Perhaps some of the features of adaptive design listed here are unrealistic at this time?

Can study protocols adapt to the unique characteristics of the participants or the participants, or the disease?

Can sponsors select patients based on the understanding of mechanisms, identification of disease pathways, ... not just cell type.

Or alter the schedule or approach to immunotherapy based on the immune characteristics of the individual subjects?

Cooperative Effort!

There's an URGENT need for competitors to pool data and share resources

- Identify and validate biomarkers
 - To enable stratifying participants by risk, molecular characteristics & targets
- Collectively sponsor molecular profiling studies?
... provide the underlying context for judging outcomes of all studies.
- Opportunity to demonstrate that drug sponsors are genuinely interested in the welfare of patients ... that it's not all about profits.

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Our group is concerned that each individual study will be too small to validate important biomarkers – and that only by pooling data can we hope to be as efficient as we can be and advance the science.

We believe that the industry needs to augment competition with cooperative efforts; to pool certain kinds of data, to share resources; and to standardize language and methods in order to make this possible.

DISCUSSION: It's not easy to merge data from different sources. Differences in protocols may lead to information that's not credible to the FDA. This highlights the importance of standardization of methods and language. See NBN Blueprint for guidance.

Make History

Where would our economy be without shared resources and standards for use, such as electric power?

Fund a National Tissue Resource

*Standardized capture, storage, analysis,
and shared access of biospecimen data*

The **National Biospecimen Network (NBN) Blueprint**
http://www.ndoc.org/about_ndc/reports/pdfs/FINAL_NBN_Blueprint.pdf

The **Cancer Genome Atlas (TCGA) Project**
<http://cancergenome.nih.gov>

*“A good hockey player plays where the puck is. A great hockey player
plays where the puck is going to be.” ~ Wayne Gretzky*

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Many leading scientists believe that there's an urgent need for a shared resource that can serve the entire research community in order to accelerate discovery and enable more efficient research: an independent National or International biospecimen network.

Some of the main services will be the standardized capture, storage, annotation, and analysis of biospecimens, ... including tracking of donors to help correlate clinical outcomes to the underlying biology of the tumor and other differences in patients.

But will a highly competitive industry support a cooperative resource? I predict that once informed, cancer patients will donate the tissue, and gladly.

The commercial independence of the resource could be essential to achieving trust and broad participation - perhaps it will need to be a non-profit entity. It should be governed by respected scientists.

Importantly, it should include strong patient and industry representation: Patient representation to win and sustain public confidence, to efficiently address consent and privacy concerns, and to foster open access to discoveries about disease pathways and biomarkers.

Strong industry representation is needed, of course, because only with industry innovation and marketing incentives can urgently needed new drugs ever reach patients.

Participation: Locating Studies for lymphoma

Providing single-click access to trials by:

- 1) Lymphoma subtype
- 2) Treatment type – with tools to locate data on outcomes, safety, and mechanisms
- 3) Treatment setting ... first line, refractory ... the circumstances of the patient
- 4) Geographic location ... studies near the patient

Asking for no identifying info

Obviously, you can't consider what you don't know to exist. And so we need to also make it easier to locate trials and to review. From our website, lymphomaaction.org, patients and physicians can easily locate lymphoma-specific studies in ClinicalTrials.gov.

Here's a screen shot of our locator service. ... From here, you can find studies by treatment type, lymphoma subtype, first line studies, new studies, and much more.

Importantly, we ask for no identifying information.

We feel that independent patient advocacy groups are ideally suited to providing this kind of service, and that an inclusive centralized database – that can be queried – is essential to enabling it. So we are thankful for ClinicalTrials.gov, and for the FDA mandate that sponsors list all trials in this centralized database.

Discussion: We also provide queries to locate reports on outcomes, safety, and mechanisms of new agents. We encourage patients to consider trials, talk about trials, consult independent experts about trials. We do not encourage self sacrifice.

Summary: Stakeholders

- **Patients**: Advocate Inform stakeholders about the urgency and the needs; inform about trials.
- **Sponsors**: Augment competition with cooperative efforts. Innovate, but also Support shared resources, standards, TCGA / NBN shared biomarker research
- **FDA**: Provide guidance on adaptive study design – stratified targeted research, validation and use of biomarkers. Guide
- **Public/Representatives**: *Listen Enable*

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This slide summarizes the roles we see for the various stakeholders.

As patients, we urge sponsors to create innovative, flexible, patient-centered trial designs and offer them to the FDA. We urge sponsors to pool data, share technologies, and standardize methods ... to advance the science by cooperative efforts – to compete vigorously with lead products, of course, but cooperate where and when you can.

Patients need to have confidence in the treatments we receive ... and I am personally thankful for the integrity, independence and leadership of the FDA. We are encouraged by the efforts of the agency to work closely with and guide the industry, and to involve and seek guidance from the patient community as well.

Probably, a main challenge and need is to raise public awareness of the importance of applying new tools and standards to delivering on the genuine promise of clinical research in the genomic era.

The Critical Path report, I think, clearly shows that competition and market incentives alone will not be enough.

Summary: Address the crisis

- **Fund** and provide expertise in support of National Tissue resources: *Standardized capture, storage, analysis, and shared access of biospecimen data*
- **Cooperate** in discovery and sharing data about the underlying biology and pathways of cancers.
- **Cooperate** in validation of biomarkers and tools that predict toxicity, response, disease risk ...
- **Study design ...**

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On this slide I've summarized the keys to addressing the crisis in clinical research

The need to create a shared infrastructure and to develop new tools.

I'll note that models for cooperative efforts and shared infrastructure are all around us. How many of us would have arrived safely without transportation standards and infrastructure?

It's clear to me that the greater research need today is not for the approval of yet another active drug, but for tests that can reliably predict safety and responses to the drugs we have, and new drugs under development.

Biomarkers

Data on variability and safety of drugs: 100,000 Americans die annually from drug toxicities and 2.2 million experience serious ADRs...Lazarou et al, JAMA, 279, 1200, 1998

... Summary: study design

Need for protocols that:

- **Address heterogeneity**: target disease pathways that can be patient-specific. Stratify participants based on molecular targets and subtypes
- Have a greater potential to **meet clinical needs of the participants in specific setting** ...
first primary, watch & wait, second-line, refractory
relative to other available protocols
- Have **flexibility** (Adaptive Design); adapt to patient differences and changing clinical circumstances
- **Utilize predictive tests, biomarkers** (Increase patient confidence), “*getting the right drug to the right patient.*”¹
- **Minimize risk** of unproductive toxicity, burning bridges, unpredictable toxicity

A key to making studies attractive or reasonable as treatment decisions will be addressing patient goals, fears, and clinical needs.

And as this audience knows well, the competition for patients is increasing; and therefore study protocols, by necessity, will have to compare favorably to your rival's, and also to all available standard treatments.

Flexibility – adaptive study design – is a positive and welcome direction.

Probably the biggest need is to address disease heterogeneity within diagnostic categories.

There's a growing consensus for the need to include predictive tests, and to develop, validate, and use biomarkers, so that we can improve the risk/benefit profile for clinical trial participants, and ultimately the standards of care.

... So that we can “get the right drug at the right dose to the right patient” as described by Dr Von Eschenbach.

Summary: Patient Interests and Concerns

Patient interests and concerns:

- Minimize risk of unproductive toxicity ... (averse to risk)
- Minimize risk of bridge burning
- **Interested** in targeted therapies that may be less toxic, and matched to the tumor's molecular profile
- **Interested** in protocols with curative potential ... when realistic.
- **HIGH interest** in immune therapies to manage or consolidate response to standard therapy ... watchful waiting: opportunity

The role of the treating physician is guide the patient ... best protocols at best time. Do what is best for patient; not to advance the science, or to help win marketing approval of individual agents.

Note: Providing incentives and finding better ways to recruit patients will not fix an underlying problem: the appeal of the clinical trial to the patient as a treatment decision.

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I want to emphasize that cancer patients will be very careful about treatment decisions. Always.

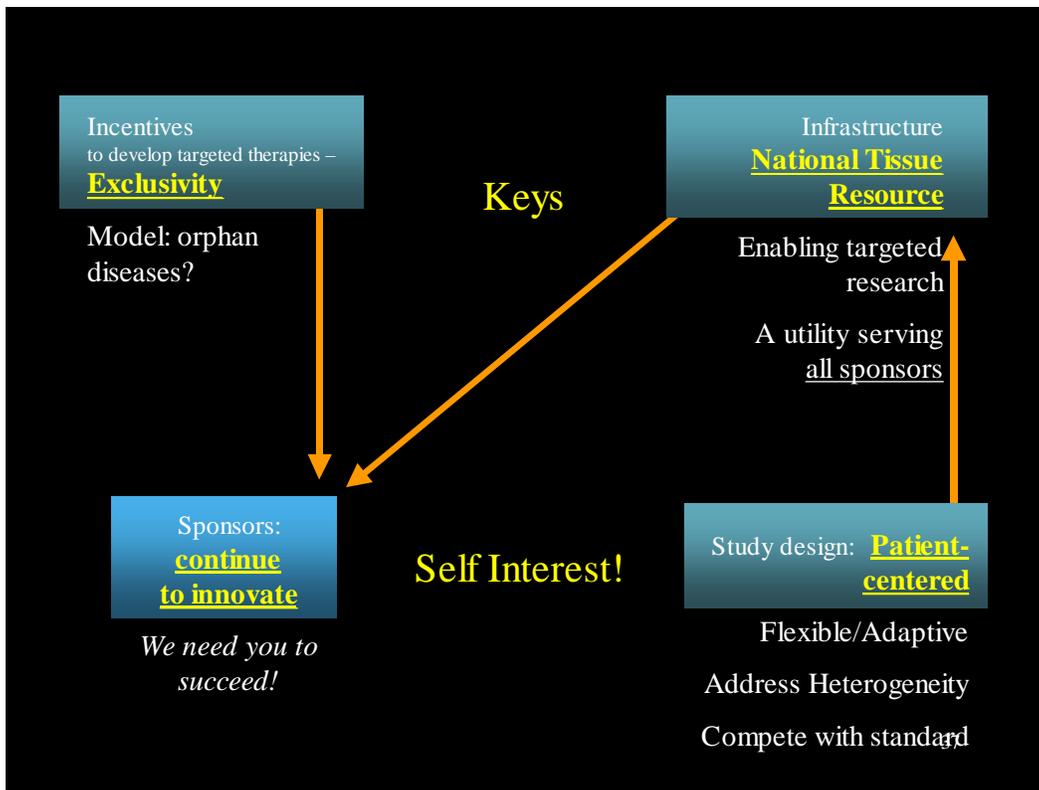
Each patient has one life to experiment with, ... and the role of the physician is to do what is best for their patient; it is not to advance the science, or to help win marketing approval of individual agents.

These are my impressions:

Therapies with low expected toxicity will enroll patients the fastest. Obviously, patients with high-risk disease need potentially curative protocols that sequence and combine complementary therapies.

Patients seeking to manage low-risk disease will not be interested in trying new single agents, unless they are targeted, or immune-based, and expected to be low toxic.

Providing incentives to physicians and seeking better ways to recruit patients – remedies often proposed by different parties – will not fix an underlying problem: the appeal of the clinical trial to the patient, and his or her physician, as a treatment decision.



A closing thought.

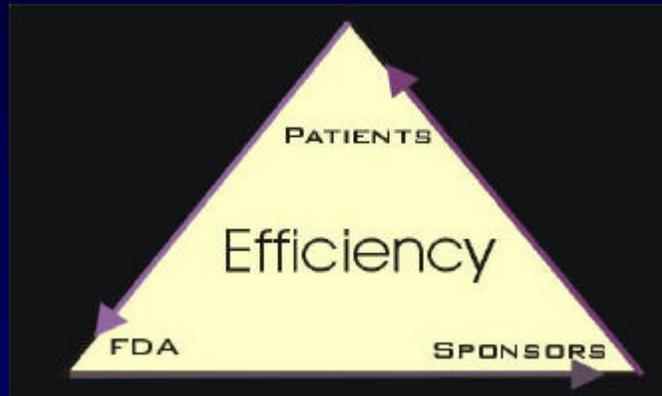
Perhaps a guiding principle for patients and drug sponsors is **SELF INTEREST**. We each need incentives:

Sponsors to innovate; patients to participate

The keys to progress and success include:

- Fund and support the infrastructure;
- Profit incentives to do targeted drug development and assessment;
- Patients to contribute tissue and to enroll in trials;
- Study design that makes trial participation a smart treatment decision.

Think like patients



Consult patients!

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Finally, I want to return to a point made earlier: That virtually every family will be affected by a serious cancer.

The scope of the problem and the current trend in clinical research calls for a new approach:

The need to provide flexible-patient-centered trials, along with the ever increasing need to think like, and to consult, patients.

Thank you all for the vital work that you do, ... and for listening. It's appreciated.