Why Enrichment is Important in AD and PD

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Outline

1. Basics of enrichment: 3 main types and how they might help in AD and PD. Need to point out that these approaches have NOT yet been used in either of these diseases.

2. Possible enrichment maneuvers to consider, focusing on prevention and disease modifying treatments, rather than the symptomatic treatment setting.

Enrichment

Enrichment is the prospective use of any patient characteristic – demographic, pathophysiologic, historical, genetic, and others – to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population.

This occurs to a degree in virtually every trial, although enrichment may not be explicit, and is intended to increase study power in 3 principal ways, by:

- Decreasing heterogeneity (noise); choosing an appropriate population, i.e. patients who definitely have the disease;
- Finding a population with many outcome events, i.e., high risk patients, or patients with relatively severe disease – prognostic enrichment;
- Identifying a population capable (or more capable) of responding to the treatment – predictive enrichment.

Kinds of Enrichment

1. Decreasing heterogeneity – virtually universal: A variety of practical steps to decrease heterogeneity (noise) are often used and include:
   - Define entry criteria carefully to be sure patients have the disease being studied
   - Find (prospectively) likely compliers (VA hypertension studies; Physicians' Health Study)
   - Choose people who will not drop out
   - Eliminate placebo-responders in a lead-in period
   - Eliminate people who give inconsistent treadmill results in heart failure or angina trials, or whose BP is unstable
   - Eliminate people with diseases likely to lead to early death
   - Eliminate people on drugs with the same effect as test drug

   In general, these enrichments do not raise questions of generalizability.

Kinds of Enrichment (cont)

Apart from efforts to decrease heterogeneity, enrichment strategies fall into two distinct types:

2. Choosing high risk patients, i.e., those likely to have the event (study endpoint) of interest – prognostic enrichment.

   This has study size implications, of course, but also therapeutic implications. A 50% change in event rate means more in high risk patients (10% to 5%) than in low risk patients (1% to 0.5%) and could lead to a different view of a drug's toxicity.

3. Choosing people more likely to respond to treatment – predictive enrichment.

   Choices could be based on patient characteristics, (pathophysiology, proteomic/genomic) or be empiric, based on patient history of response to similar drugs, early response of a surrogate endpoint (e.g., tumor response on some radiographic measure), or past response to the test drug (randomized withdrawal study), discussed further later.

Enrichment – High Risk Patients

In one way or another, it is routine to try to find people at high risk of an event or high likelihood of progression so that an intervention will have events or progression to prevent. This is common in both oncology and CV medicine and there are growing possibilities:

- Breast or ovarian cancer prevention in people at high risk genetically or who have already had a tumor;
- Outcome studies of lipid-lowering agents in people with hx of AMI, very high LDL cholesterol, low HDL, or elevated CRP;
- Studies of anti-platelet therapies in angioplasty patients, who have a high rate of acute coronary events.

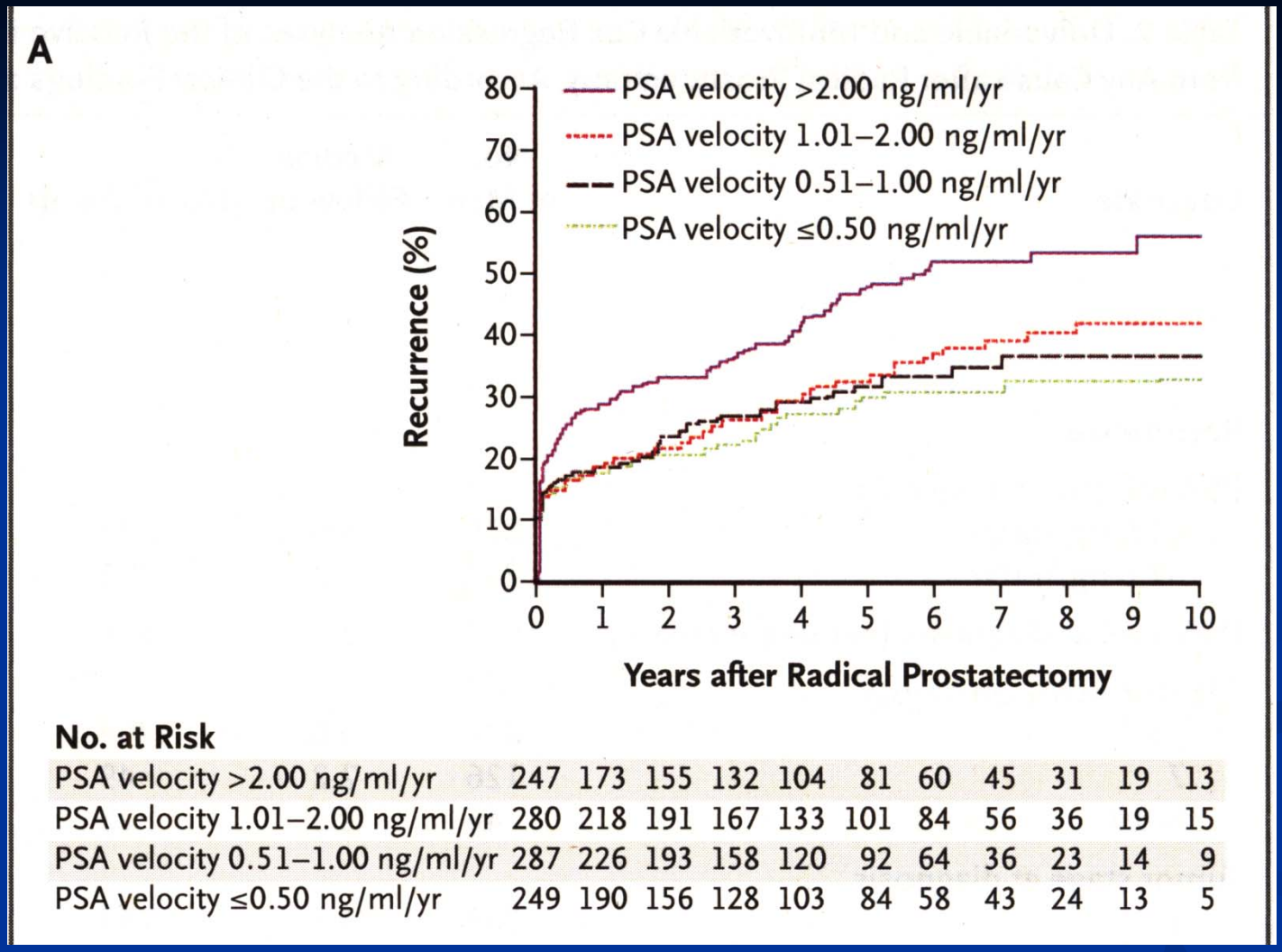
There is great potential for pharmacogenomically or proteonomically identifying high risk patients, e.g., in Alzheimer's Disease, or discovery prognostic MRI or clinical findings.

Enrichment – High Risk Patients

1. Oncology

   Potential selection method for frequent endpoints:

   D'Amico reported [NEJM 2004; 351:125-135] that in men with localized prostate Ca, following radical prostatectomy, PSA "velocity" (PSA increase > 2 ng/ml during prior year) predicted prostate Ca mortality almost 100% over a 10 year period. There were essentially no deaths from prostate Ca (many from other causes), even though recurrence rates were not so different (NB; not used yet).

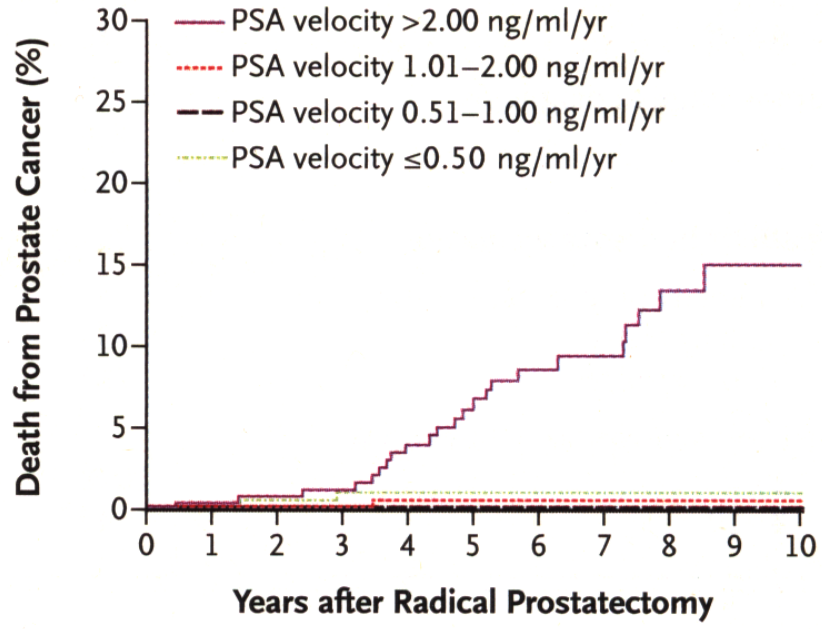


No. at Risk

PSA velocity >2.00 ng/ml/yr	247	173	155	132	104	81	60	45	31	19	13
PSA velocity 1.01–2.00 ng/ml/yr	280	218	191	167	133	101	84	56	36	19	15
PSA velocity 0.51–1.00 ng/ml/yr	287	226	193	158	120	92	64	36	23	14	9
PSA velocity ≤0.50 ng/ml/yr	249	190	156	128	103	84	58	43	24	13	5

Kaplan-Meier Estimates of Disease Recurrence (Panel A) after Radical Prostatectomy, According to the Quartile of PSA Velocity during the Year before Diagnosis

C



No. at Risk

PSA velocity >2.00 ng/ml/yr	262	257	248	226	187	157	123	92	60	36	22
PSA velocity 1.01–2.00 ng/ml/yr	288	275	248	229	194	158	131	91	58	36	20
PSA velocity 0.51–1.00 ng/ml/yr	289	281	260	227	176	131	94	55	36	18	11
PSA velocity ≤0.50 ng/ml/yr	256	236	200	163	139	108	81	61	34	20	9

Kaplan-Meier Estimates of the Cumulative Incidence of Death from Prostate Cancer (Panel C) after Radical Prostatectomy, According to the Quartile of PSA Velocity during the Year before Diagnosis

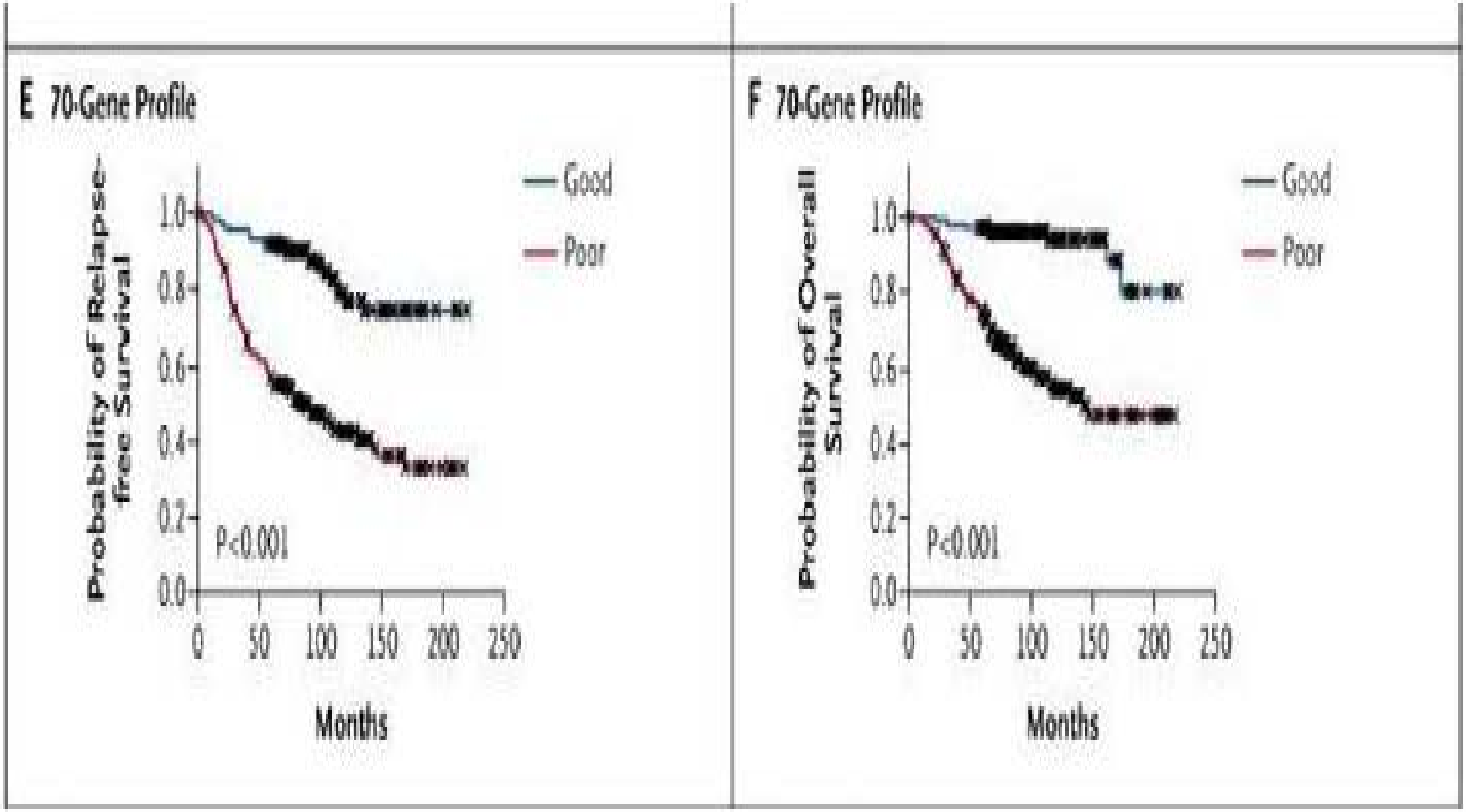
Enrichment – High Risk Patients

1. Oncology (cont)

Fan, et al [NEJM 2006; 355: 560-69] recently applied 5 different gene-expression profiling approaches, intended to predict breast cancer recurrence rates, to a 285 patient sample treated with local therapy, tamoxifen, tamoxifen plus chemo, or chemo alone.

Four of the 5 methods had high concordance and a striking ability to predict outcome and the differences were very large. One of them, a 70 gene profile, is shown on the next slide. The implications for patient selection are obvious, whether the endpoint is recurrence or survival. Studies should select poorer prognosis patients to have a better chance of showing a drug effect.

Recent approval of MammaPrint, an in vitro test based on gene expression profile will facilitate such selection.


E 70-Gene Profile
Probability of Relapse-free Survival
1.0
0.8
0.6
0.4
0.2
0.0
P<0.001
0
50
100
150
200
250
Months
Good
Poor
F 70-Gene Profile
Probability of Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
P<0.001
0
50
100
150
200
250
Months
Good
Poor

Enrichment-High Risk Patients

2. Cardiovascular

Long routine to choose, in outcome studies, patients at high risk (secondary prevention, post-AMI, or stroke, very high cholesterol, very severe CHF, undergoing angioplasty) so there will be events to prevent. For example:

- CONSENSUS (enalapril) in NYHA class III-IV patients studied only 253 patients, showing dramatic survival effect in only 6 months study. Mortality untreated was 40% in just 2 months, and treatment showed a 40% reduction. Later studies needed many 1000's of patients;
- First lipid outcome trial (4S - Simvastatin) in a post-MI, very high cholesterol population: 9% 5 year CV mortality, needed only 4444 patients for a mortality effect. Later trials larger, used composite endpoints.

Selection of High Risk Patients

3. Other

Identifying people at high risk is especially important in "prevention" or risk reduction efforts. Apart from the CV risks we know about, there may be genetic predictors of risk (e.g., for Alzheimer's Disease or particular cancers) or early signs of Alzheimer's Disease (people with minimal brain dysfunction or other abnormalities). This is especially critical if intervening early is important.

Selection of Likely Responders (Predictive Enrichment)

Identifying the people who will respond to a treatment, then formally studying them, greatly enhances the power of a study and has clear implications for how a drug will be used.

It can be especially critical when responders are only a small fraction of all the people with a condition, e.g., because they have the "right" receptor. In such a case finding an effect in an unselected population may be practically impossible.

Selection can be based on understanding of the disease (pathophysiology, tumor receptors) or it can be empiric (e.g., based on history, early response, response of a biomarker).

Selection of Likely Responders

Pathophysiology

- Hypertension can be high-renin or low-renin. High renin population would show a much larger effect than a mixed population to ACEIs, AIIBs, or BBs.
- We study antibiotics in bacterial infections sensitive to the antibacterial or, if not identifiable initially, we examine the subset that had the relevant organism.
- A well-established genetically determined difference could be the basis for a pathophysiologically selected population. Many tumor genetic or surface markers are related to well-understood effects on enzymes or growth stimulus: Herceptin for Her2+ breast tumors; selection of ER^+ breast tumors for anti-estrogen treatment, many other receptor markers.

Selection of Likely Responders

Even if pathophysiology is unclear, likely responders could be identified by an initial short-term response, an empiric approach. There is a history of this:

- CAST was carried out in people who had a 70% reduction of VPB's. Only "responders" were randomized.
- Trials of topical nitrates were carried out only in people with a BP or angina response to sublingual nitroglycerin.
- Anti-arrhythmics were developed by Oates, Woosley, and Roden by open screening for response, then randomizing the responders.
- Every randomized withdrawal study has this characteristic.
- History of response to a class.

Predictive Enrichment – Pathophysiology or genetic characteristics

1. Only people who make the active metabolite (clopidogrel)
2. Only people whose tumor takes up the drug (History, test for I 131 uptake in thyroid tumor to choose dose)
3. Effect on tumor metabolism, e.g., glucose uptake
4. Proteomic markers or genetic markers that predict response – recent cystic fibrosis drug
5. Virus genotype – hepatitis c drugs boceprivir and telaprivir treat genotype 1

Plainly, the wave of the future in oncology (Herceptin; imatinib inhibits c-KIT, a receptor for tyrosine kinase, that is mutated and activated in most GIST patients; vemurafenib in melanoma effective in patients with activating mutation $BRAF^{V600-E}$.

So…What about AD & PD

The heterogeneity reducing aspects of enrichment are plainly applicable. Patients in a trial in early stage AD need to be able to perform the neuropsychological tests that will be used and give consistent results, should probably not have concomitant illnesses that could also affect mental function and performance (e.g., bipolar disease, severe CHF).

Attempts to use prognostic enrichment depend on whether the severity of disease is both prognostic and predictive. Obviously, it is likely that people who have already developed clear, even if early, signs of dementia are more likely than others to progress, so their inclusion is critical to assure a high rate of a progression manifestation that could be measured in the trial.

So, What About AD & PD (cont)

Indeed, without progression the study must fail. There is concern, however, that more advanced patients will no longer be able to respond to treatment, which might work only in early stages, e.g., before there is ANY sign of cognitive impairment. (NB, this is clearly not the case in cardiovascular disease).

Studying Early Disease

Thus, if overt dementia is "too late," there will need to be ways to find "early," pre-morbid patients. Our recent draft guidances on drugs for early stage disease suggest that diagnosis of MCI may find patients early enough to respond and suggests addition of anatomic evidence to:

1. Improve the "somewhat uncertain" characterization of MCI (prognostic enrichment; only MCI will progress to AD)
2. Make it more likely that MCI is the consequence of AD rather than other early dementias.

The second feature is, in fact, an effort at predictive enrichment, i.e., trying to identify patients with a disease cause (AD) that could respond, unlike vascular dementia.

Studying Early Disease (cont)

If even early dementia is "too late," it might be possible to utilize genetic predictors or beta-amyloid and tau protein levels in the brain even before there is any cognitive impairment, perhaps in people with a family history of dementia, to predict likely progression (prognostic enrichment), but of course, the problem is that cognitive impairment could be quite delayed. This prognostic effort is, at the same time, an attempt at predictive enrichment, i.e., finding patients still capable of responding.

Don't R/O Later Disease

Given the failure of all attempts to date to delay progression of AD or PD it is understandable that the view would arise that "it was too late," but that conclusion may be premature, merely reflecting the absence of any effective treatment.

As noted, in CV disease it has been easiest to show benefits in advanced disease, both because studies of these patients are prognostically enriched and because effect sizes are at least as large. In AD and PD, people with disease continue to progress, surely because of further anatomic deterioration.

So don't give up on advanced disease, a plainly prognostically enriched population.