INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

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"*Evidence-based" is now a popular buzz phrase in medicine. Diagnostic procedures, invasive interventions and pharmaceutical treatments should be evidence based. Mainstream medicine would like us to believe that in fact we now live in a new era where this is more or less the case and medical students are properly indoctrinated regarding the importance of applying this yardstick to practically everything they do and certainly use it to reject most of alternative medicine or anecdotal evidence. In spite of serious limitations, meta-analysis is the supreme court of medicine. The origin of this evidence involves studies, mostly done during the last 20 years, and mostly sponsored by the pharmaceutical industry or the device industry. They have the deep pockets necessary to support the requisite large clinical studies. But over the past decade a large body of evidence has been uncovered suggesting that results generated by industry sponsorship tend to favour the sponsor, and that the published accounts are biased in favour of efficacy and downplay side effects. The techniques involved have become common knowledge and include design bias, multiple trials with predictable outcomes, selective publication, fraud and scientific misconduct. Clinical studies do not in some cases seek truth but rather evidence obtained by questionable methods to support the assertion that the product is safe and works. This becomes part of the input data required for regulatory approval. Marketing takes advantage of publication bias, spin, ghost writer enhanced credibility, and biased speakers involved in continuing medical education. There is the potential for deception associated with the drug-rep model of providing product information to practicing physicians. Large drug companies continue to be successfully prosecuted for illegal off-label promotion of their products but have paid fines that are small only in comparison to the profits made on the products involved. Evidence for the above picture is extensive.*

Many solutions have been suggested and some implemented with limited success. An attempt has been made to force the pre-trial registration of clinical trials and timely, complete post-trial reporting. Journals are trying to discourage ghostwriting of papers providing clinical trial results. Some journals attempt to force conflict of interest disclosures. Data reporting standards have been tightened. However, some critics view these measures as inadequate and even dysfunctional and call for an overhaul that turns over all clinical trials to agencies or organizations that have no ties with the industry. Since the amount of money required is enormous, this would presumably require the drug companies to provide huge sums with absolutely no strings attached. It would require recruiting clinical investigators with no present or perhaps even prior industrial associations.

Highlights

Those who believe this is possible may not be taking into consideration the extent to which Big Pharma has infiltrated all aspects of medical research and marketing. Today, journal editors claim that if one wants high quality reviews written by top experts, this will frequently require authors with conflicts of interest. Governments and other organizations assembling expert panels to develop guidelines appear incapable of recruiting a group which does not include some, if not a majority who have wide-ranging conflicts of interest. In the US, the FDA expert review panels frequently include individuals who have direct conflicts of interest. Non-pharmaceutical agencies and

organizations, attempting to initiate clinical studies on the scale envisioned by those proposing that this should be the only way clinical trials are conducted, would almost certainly have great difficulty recruiting the required number of top clinical scientists free of existing or potential bias and conflicts of interest. Even some individuals administering these presumably neutral, unbiased agencies and organizations have either present or past associations with the pharmaceutical industry and the world's capitals are saturated with drug company lobbyists. Even academics with no associations with industry can be driven by the desire to produce important, positive results publishable in high-profile journals. This is the traditional route to promotion, grants, research chairs, and membership in honorary societies.

What is at stake here could not be more important. It involves the real merits of therapies and interventions, some of which almost all of us will have to consider sooner or later. It also involves a substantial fraction of the money spent (or wasted) on health care, either private or public.

If you need to restock your supplements, please remember that by ordering through the on-line vitamin store you will be helping to maintain the web site and the publication of IHN. You can find the store at http://www.yourhealthbase.com/vitamins.htm.

Wishing you and your family good health,

William R. Ware, PhD, Editor

ELEVATED CHILDHOOD CHOLESTEROL BRING ON THE STATINS

The National Heart, Lung and Blood Institute (NHLBI), which is associated with the NIH has just come out with guidelines for pediatric cardiovascular risk reduction. Chapter 9 of their report deals with the NHLBI position on lipids and lipoproteins, the feature subject of this issue of the Newsletter. The version with references is not easy to find.[1] See the cited link which contains the lipid chapter with references. Just change the chapter number to see the complete guidelines. These guidelines are similar to those published in 2008 by the American Academy of Pediatrics which has been promoting pediatric use of statins for some time.[2]

Children from birth to the time they approach adulthood represent a very special class in our society. These young individuals cannot nor can they be expected to give informed consent. This must be given by parents who in many cases lack the information required to make intelligent, informed judgements. Children are special since throughout childhood and well into adolescence they are undergoing complex biological development processes which are vulnerable to adverse influences by exogenous chemicals including drugs. But children are viewed by the drug industry as a huge market only partially exploited. Until recently, Merck was working hard to get each U.S. state legislature to make school entry impossible, for example into the upper grades, without having a HPV vaccination. They recently abandoned this after considerable backlash but not before two states and the D.C. took away from parents the right to decide unless they were able to meet the op-out requirements. Another example, as discussed on several occasions in this Newsletter, concerns depression and ADHD medications. They represent one pediatric marketing triumph, although this may be unravelling, as also discussed in our Newsletter, now that a few prominent psychiatrists have started promoting the view concerning over-diagnosis, overtreatment, serious side effects and limited efficacy.

Cholesterol and LDL targets for children and the associated statin therapy represents a marketing frontier. All that is required is more guidelines bearing some stamp of official approval that pediatricians and general practitioners can follow. The NHLBI guidelines just issued seem to be a perfect example. At the beginning of the lengthy NHLBI report, a list of members of the expert panel is presented along with their potential conflicts of interest. Seven of the fourteen members, including the chair of the panel, declared ties, frequently multiple, with drug companies. In the past, this situation has always prompted criticism from critics and raised questions as to the interpretation and completeness of the cited literature and the potential for "spin" in framing the guidelines. The issues involved in this particular case will be discussed in some detail since your editor feels very strongly

that medicating children should be approached with extreme caution and only if the benefits are highly significant and clearly outweigh by a wide margin the risks. Unfortunately, when long-term medication of children is involved, the risks in fact are generally unknown and merely surmised from short-term studies. Extrapolation from adult studies remains to be justified.

CHILDHOOD DYSLIPIDEMIA AND ATHEROSCLEROSIS

Atherosclerosis is almost always a prerequisite precursor for coronary heart disease and cardiovascular disease. In dealing with the risk of serum lipids and cardiovascular risk in children, all that can be examined are biomarkers since acute events are extremely rare and there is a reluctance to use CT scans to examine the coronary atherosclerosis issue. The connection between coronary atherosclerosis and cholesterol is fundamental to the NHLBI guidelines. The NHLBI report presents the evidence justifying their recommendations, citing studies they claim significantly relate cholesterol levels and LDL levels to childhood atherosclerosis in its various manifestations. The impression created in Chapter 9 is that the science is clear. The panel cites 12 studies that appear directly relevant see (website link for references). If studies have been omitted from the report, it is likely that they did not strengthen the guidelines. Five autopsy studies are cited. The *minimum* age is 15, in sharp contrast to the guidelines which discuss children form 2 up and recommend routine screening for lipid risk factors starting at age 9 and earlier if patient history provides justification. In 4 of the studies, lipids were not even considered or they were included in risk scores without examining the relative importance of the lipid, and thus did not relate to the question of the presence of a positive lipid association. One autopsy study provided only Spearman coefficients which included LDL, but with no multivariate analysis or odds ratios adjusted for confounders. The one study that included a multivariate analysis used only non-HDL cholesterol and thus did not take into account TGs as a confounder. LDL was never mentioned. Thus the autopsy studies appear almost entirely irrelevant or at least do not provide any convincing support for the connection between serum cholesterol or LDL and childhood atherosclerosis, which the NHLBI guidelines described as evidence based.

Only one study cited used CT scan data (EBCT) and thus coronary calcium as a measure of atherosclerosis, but for the age group from 8 to 18, no cholesterol data whatsoever was presented or included in the analysis, and thus the citation is irrelevant to guidelines since this is the targeted age group.[3]

Four studies cited employed carotid artery intima-media (cIMT) thickness as the measure of the association of atherosclerosis with blood lipids. For two, the minimum age was either 20 or 24, and again one can question the relevance of these citations to guidelines that start with 2-year olds and set targets for LDL starting at age 9. The other two studies examined the association between cardiovascular risk factors measured in childhood and cIMT measured in adulthood. In one study, risk variables measured at or before 9 years old were not generally found to be associated with adult increased cIMT, although this fact was buried in the text. The other study found that for adults, the cIMT increased with LDL levels. However, for adults, coronary atherosclerosis is independent of LDL, and thus one can question the result as relevant, aside from reinforcing the evidence regarding the very poor correlation between carotid and coronary atherosclerosis.[4] Furthermore, studies cited attempt to demonstrate clinically significant associations by measuring parameters in childhood and then look at cIMT in adulthood appear subject to numerous possibilities for confounding.

The guidelines would have every child or adolescent screened for blood lipid levels starting between age 8 and 11. Children 2-8 years would be screened if family history raises concerns or if they have certain health issues. Elevated levels would potentially be subject to treatment targets. Yet, there does not appear to be any evidence, contrary to the assertion of the NHLBI report, that the prevalence or progression of arterial atherosclerosis in children is associated with total or LDL cholesterol. The evidence cited in the guidelines, while abundant in terms of references, is lacking when the papers are downloaded and examined. Critics would probably comment that this has been a common situation for decades with many guidelines. Some readers of the guidelines are not even offered the references, and if they are, it is unlikely they will examine the actual studies in detail. Many do not have full-text access. Reading free abstracts on PubMed is not enough! This applies to both concerned laypersons and professionals. For the nonprofessional, analysing clinical or

observational studies can be a severe challenge. This is an important *raison d'être* for the flourishing of modern medical mythology.

Thus where is the solid evidence on which to justify an intervention (statins) which inhibits a pathway (the acetyl and mevalonate pathway) which leads to a number of critical biochemicals and also to other important pathways? There is a huge trickle-down effect. And we are talking about long-term inhibition. And this during the highly complex and far from totally understood process of childhood development, of course including the development of the brain. As discussed below, the studies presented to prove that the intervention is safe are of necessity very short and one can argue, should be ignored. It is remarkable that parents would even allow children to participate in such trials. The NHLBI guidelines are recommending an intervention where there is no applicable or truly relevant safety data. And this is for children who have no say in what is happening to them. Reading books such as *The Statin Damage Crisis* by Dr. Duane Graveline, MD should scare some parents even though the evidence presented pertains to adults. In fact, it is quite possible that these drugs are more dangerous for children. Also, can one accept that statin intervention is safe for children as they go through the process of physical and mental development when that therapy has just been given new "black box" warnings from the FDA concerning serious side effects including enhanced risk of diabetes?

THE NHLBI BLUEPRINT. PARENTS TAKE NOTE

The primary issues for the guideline formulators were when a blood lipid panel should be obtained for children (screening), what levels of blood lipids should be a cause for concern, what lipid targets are appropriate and how should they be attained. First the screening issue.

According the NHLBI, children 2 to 8 years should be screened if there is a family history of heart disease or stroke in parents, grandparents, aunt/uncle or sibling, provided the manifestations occurred prior to 55 for males and 65 for female, or if a parent has a total cholesterol ≥ 240 mg/dL, or if the child has diabetes, hypertension, is obese, smokes, or has a special medical condition that puts them at moderate or high-risk of CVD.

For children between 9 and 11, universal screening is highly and unconditionally recommended. For those between 12 and 16, screening should be done if any of the criteria listed above for the 2-8 age groups are met. For those 17-21, universal screening is again recommended.

It can be argued that screening should be recommended only in situations where the markers or parameters measured, in this case blood lipids, are evidence based risk factors for a disorder for which effective interventions exist and where the benefits of the intervention clearly outweigh the risks. Otherwise, why screen? The NHLBI report lists acceptable levels of blood lipids for children and adolescents. The guidelines give < 170 mg/dL for TC and < 110 mg/dL for LDL. Where is the evidence? As discussed above, the evidence for childhood serum lipids being risk factors, unless they are highly abnormal, appears lacking in the context of CHD/CVD. Thus these values must be considered hypothetical and not evidence based. One is reminded of the recent criticism of LDL targets in adults which are now criticized for not being evidence-based.[5]

At this point the guidelines become very complicated. Levels of the various blood lipids are given which lead to the use of algorithms to decide therapy. Readers are referred to Figures 9-1 and 9-2 of the report linked above for details. The recommendation for statin therapy can be triggered at levels as low as 130 mg/dL for children as young as 9 if other risk factors are present. If TGs as well as LDL are high, TGs are also targeted, although drug therapy is reserved for highly elevated TGs. For children with LDL ≥ 130 mg/dL to 189 mg/dL and no other risk factors, a lifestyle-diet approach is recommended with repeat lipid testing every 6 months. But this approach traditionally fails. Do practitioners then turn to statins? Probably.

Drug interventions should require convincing evidence that benefits far outweigh risks, especially for this highly vulnerable group. The NHLBI guidelines present a list of 20 pediatric statin safety studies

available in the literature, presumably as of 2011. The list omits references. The studies had the following characteristics:

- They involved a very small number of subjects and some used the same cohort to test different doses.
- All involved children who had been diagnosed with genetically caused highly elevated cholesterol levels (familial hypercholesterolemia or FH), hardly representative of those with somewhat elevated cholesterol or in fact the majority of the group in question in the context to the NHLIB guidelines.
- Median study length was 24 weeks, the shortest 8, the longest 48.
- None involved endpoints for comparison concerning benefits hypothesized to be associated with achieving target values of LDL.
- These studies showed the expected changes in lipid levels, i.e. statins do indeed inhibit the acetyl and mevalonate biochemical pathway in children.

It can be argued that FH must be considered as a special disorder, not just a situation characterized by highly elevated cholesterol, and any data collected from adults with FH cannot be extrapolated to children. Furthermore, when the association between various types of coronary plaque and cholesterol have been examined in adults by the most modern computed tomography coronary angiography, cholesterol was not found to be a risk factor after multivariate analysis for either non-calcified coronary plaque or mixed calcified and non-calcified plaque.[6] If one is going to extrapolate from adults to children, why not extrapolate this? For children with elevated cholesterol due to FH, there is no evidence that cholesterol lowering with statins has any impact on coronary heart disease, either silent or manifest by acute events. Extrapolation from adults would in fact suggest that lowering cholesterol is in fact not important.

The studies that have been done are very short and of course did not examine acute cardiovascular events. Thus these studies address nothing more than biomarker changes and very short-term side effects. The validity of the monitoring or evaluation of side effects is not clear. The study periods were too short and measures to insensitive to yield answers to key questions regarding developmental or neurological adverse effects or any adverse effects that might show up later. Parents should ask themselves, am I going to allow my child to be medicated when the impact on his or her mental or physical development in future years is totally unknown? This is in sharp contrast with the adult situation. Statins reduce the risk of acute events in asymptomatic adult populations including those with diabetes with elevated TC or LDL, but it is only by a minute amount. Some children have elevated TC or LDL. Is the justification for treating them with statins, because this intervention produces very small benefits for some asymptomatic adults? Adult studies show greater impact on acute events in those with established CVD, especially CHD, but the absolute risk reductions are only in the range of a few percent rather than the 1% seen with asymptomatic individuals, but this is also not relevant to the question of treating children. As discussed several times in this Newsletter, these beneficial effects in adults may also have nothing to do with lipid lowering.

One argument used for therapy is that elevated childhood levels of TC and LDL correlate with young adult levels and adult levels. Therefore, the elevated levels in children are bad and must be treated. The correlation, if real, is not strong. The counter argument; TC and LDL are very weak or insignificant predictors of CVD events or mortality in adults and thus why is this valid argument for treating children?

The rationale for statin therapy in children is presumably to prevent atherosclerosis or slow its progression. Statin therapy has been shown to have no influence on the prevalence or progression of coronary atherosclerosis in adults.[7,8] One can then ask, why is it expected to have this beneficial effect for children. There are no significant studies addressing this issue in children and thus the therapy is not, in the usual sense of the term, evidence-based. A family history of CHD/CVD may increase the risk of children developing related disorders, but there is no evidence that treating this risk with a therapy that is ineffective for controlling adult coronary atherosclerosis will in fact work in the pediatric setting.

Childhood development is extraordinarily complex and continues until late adolescence. One can argue that during this critical period it is not a good idea to introduce therapy involving chemicals unknown to human biochemistry which potentially will be taken for a number of years without convincing evidence of either benefit or very strong evidence of the absence of long-term adverse effects. The former requires randomized controlled trials with event endpoints—an impossibility. The demonstration of the absence of adverse effects is equally impossible since a complete analysis of the impact of therapy on childhood development and the demonstration of the absence of adverse effects that become apparent only after a number of years cannot be achieved.

It is important to note that the importance of highly elevated cholesterol levels in children with FH is not being downplayed or presented as unimportant. But this is a distinct disorder of a complex nature with cardiovascular risks such as coagulation defects which may be unique. But for adults with FH, atherosclerosis as quantified by age adjusted coronary calcium score does not correlate with cholesterol levels.[9] Thus focusing on childhood cholesterol may be a blind alley.

Thus the critical question parents must confront. Do they allow their children to be exposed to a drug that inhibits a large number of important biochemical pathways, has well documented risks in adults, claimed by some to be vastly under-reported and which are potentially serious and occasionally fatal, and to a drug that has totally unknown mental and physical long-term risks for the developing child? Does one initiate statin treatment for children when we are now seeing articles appear in peer reviewed journals with titles such as *The cholesterol hypothesis: time for the obituary?*[10] Thus parents would appear to be entirely justified in saying, leave my kid alone and keep your drugs for adults. You are treating a hypothetical situation, and this a without a convincing risk vs. benefit argument.

GROWING EVIDENCE OF OVERDIAGNOSIS AND OVERTREATMENT OF ADHD

Three recent studies have employed an interesting approach to this question. The latest, just published in the Canadian Medical Association Journal, considerably strengthens this view.[11] The Canadian researches made use of the fact that entry into kindergarten or grade 1 has a date of birth cut-off of December 31 in British Columbia. This ensures that each class will have a more or less even distribution of ages covering one year, with the youngest in a class born in December. Universal public health care means Provincial health databases provided comprehensive data regarding both the diagnosis and treatment of ADHD. It was found that boys and girls born in the month before the cut-off were 30% more likely to be diagnosed with ADHD and 41% more likely to receive ADHD medication than the children born in January. This effect persisted with relatively stable strength over an age range of 6 to 12 years. The prevalence of diagnosis and treatment was considerably higher in boys as compared to girls and increased over time for children of both genders. These results are consistent with those found in two U.S. studies, although the Canadian results are much more clear-cut.

These results suggest that behavior patterns common to the youngest members of a class, in contrast with those of the older children in the same class, influence teachers to entertain and pursue the possibility of ADHD to a greater extent in this younger group. If one assumes that the younger children are simply acting normally under the circumstances, then the possibility of overdiagnosis and overtreatment is strengthened considerably. Critics of this point of view who quote chapter and verse from the DSM-IV, the psychiatric diagnostic bible currently in use, to prove that those diagnosed are in fact abnormal should be made aware of the view of the chairman of the DSM-IV writing program, Dr. Alan Francis from Duke University, who now admits to unintentionally creating an epidemic in the overdiagnosis and overtreatment of ADHD due to the content of the sections of the manual covering this disorder (*Los Angeles Times*, March 1, 2010).

The authors of the Canadian study also comment on the potential harm associated with overtreatment. They point out that children unnecessarily are exposed to adverse effects related to sleep, appetite and growth and in addition to an increased risk of cardiovascular events. Readers of this Newsletter and the books cited in discussions of the harms of ADHD medications will realize that the Canadian researchers have presented a rather conservative view of the potential harms. Parents interested in an in-depth discussion of the adverse effects of ADHD drugs are strongly encouraged to read the books of Peter Breggin, M.D.[12,13]

Finally, the researchers advise that a child's behavior should be examined in the context of multiple environments, especially those outside of school when assessing the possibility of ADHD. This still does not eliminate the adverse impact of the ADHD definition and symptom list in DSM-IV.

WARNING REGARDING STATIN RISK FROM THE FDA FINALLY!

On February 28, the FDA issued a formal warning regarding risks associated with statins.[14] Their press release listed the following problems:

- Liver problems with the following symptoms: unusual fatigue, loss of appetite, upper belly pain, dark-colored urine or yellowing of the skin and the whites of the eyes.
- Memory loss and confusion, amnesia, forgetfulness, and memory impairment.
- Increases in blood sugar levels and glycosylated hemoglobin (HbA1c).

This warning comes soon after recently reported studies linking statins to the risk of type 2 diabetes. These were covered in an earlier Newsletter.

Contrary to the impression provided by the media coverage of this event, the actual FDA document treats the above as a class effect. The media confused the issue by providing examples of the most popular statins, which gave the impression that the cited drugs are the only ones that now carry the warning.

The FDA also issued a special warning about drug interactions with Lovastatin and provides dose limits or the advice to avoid this statin when the patient is taking one or more of a variety of prescription drugs. Readers taking Lovastatin should download the FDA press release cited above and discuss the matter with their physician.

It is noteworthy that the nature of the adverse event reporting system and its notorious under-reporting, combined with the common practice, documented in court records, of industry suppression of adverse side effects, suggests that the evidence on which the FDA based its warnings represent only the tip of an iceberg.

The website www.theheart.org which caters mostly to the cardiology community, undertook a survey of reactions to the FDA announcement. The results for two questions are interesting.

	Not Concerned	Somewhat	Very
Concern about diabetes	33%	42%	24%
About cognitive/mental	46%	32%	21%

The FDA warning appears to have had some impact. Also, for elevated HbA1c levels, 13% claimed to see this often. For signs of cognitive effects, 7% admitted seeing them often. These answers should be interpreted in light of the following comment quoted by *heart.org*. Dr. Eric Topol (Scripts Clinic, La Jolla, CA) was quoted as pointing out that the recognition of the cough associated with ACE inhibitors was not recognized until a case series was published in the *Lancet*. Now it is accepted as a common

side effect well known to physicians and many users of this class of drug. To quote Topol, "what the mind doesn't know, the eyes do not see." Thus a survey asking how often doctors see an association they are not looking for involving a common disorder must set a very low lower limit on the true prevalence.

http://www.yourhealthbase.com/vitamins.htm

NEWS BRIEFS

ASPIRIN AND VASCULAR EVENTS

Another meta-analysis of aspirin, vascular and non-vascular outcomes and bleeding risk has appeared.[15] The results confirm earlier studies and had a mean follow-up of 6 years and 100,000 participants. For total CVD events, the number needed to treat with prophylactic doses of aspirin to prevent one event (NNT) was 120, mostly due to non-fatal heart attack (NNT = 162). There was no significant reduction in CVD or cancer mortality. The incidence of non-trivial bleeding events was such that the number need to treat to harm one individual was 73. The authors draw the obvious conclusion that the risk of harm outweighs the risk of benefit, and recommends against this use of aspirin. This is consistent with other studies reported in this Newsletter. Recent TV ads provide quite a different picture.

ALCOHOL AND STROKE IN WOMEN

A report has just been published which examined the association between alcohol consumption and the risk of stroke in women.[16] The data were from the famous Nurses' Health Study and involved over 83,000 women followed from 1980 to 2006. Self-reported data on alcohol consumption was collected every 4 years. This is important. On constantly sees studies where consumption data is only collected once and the follow-up is 10-15years. Hazard ratios were obtained by multivariate analysis adjusting for 17 covariates. Statistically significant fully adjusted results found modest alcohol consumption protective for total stroke incidence up to 15g/day (about 1 drink). Treating alcohol consumption as a continuous variable produced a J shaped curve with maximum protection around 15 g/day and the protective effect no longer statistically significant beyond 28-29 g/day. This study was underpowered at high levels of consumption. The authors remark that these results are consistent with guidelines of the American Heart Association which suggest a modest inverse association between the risk of total, ischemic and hemorrhagic stroke at levels of ≤ 1 drink per day.

MORE EVIDENCE AGAINST SUGAR-SWEETENED DRINKS

A study just published, which is part of the ongoing Health Professionals Follow-up Study, has examined the association between sugar-sweetened beverages and incident coronary heart disease (CHD) defined as fatal and non-fatal heart attacks.[17] Over 42,000 men were followed for 22 years with food frequency questionnaires ever 4 years and state of health and lifestyle ascertainment every 2 years and fatalities identified from the National Death Index. Men in the top quartile of consumption (median of about one drink per day—range 4.5/week to 7.5/day) had a 20% relative risk increase in the CHD endpoints which was reduced to 18% after correcting for a wide variety of confounders. They also found a positive association with a number of inflammatory markers and as well increased triglycerides and decreased HDL, all of which may provide insight into the mechanism. Null results were obtained for artificially sweetened beverages. The results were consistent with a number of

other studies including the Nurses' Health Study. NOTE: No distinction was made between beverages sweetened with cane or beet sugar and those sweetened with high-fructose corn syrup.

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The Prostate Monitor
Editor: William R. Ware, PhD

Reviews of recent studies from the peer-reviewed literature

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This issue of the Prostate Monitor is entirely devoted to the new PCA3 test which has just been approved by FDA in the US to assist in decision-making in regard to repeat biopsies in cases where there is considered to be a high probability that the results are wrong. The aim is to decrease the number of unnecessary repeat biopsies by refining the pre-biopsy assessment by adding this new test. This is an example of the ongoing search for new prostate cancer biomarkers that do not have some of the problems associated with the PSA test. In the discussion of the test, we will also deal with the "off label" use of the test to assist in the decision to conduct an initial biopsy.

The FDA approval is for a commercial test called Progensa® from the company Gen-Prob. This test will probably rapidly gain popularity since there is extensive literature associated with its use and it does appear to offer significant advantages.

Wishing you good health,

William R. Ware, PhD, Editor

You can order *The Prostate and Its Problems* at

http://www.yourhealthbase.com/prostate/book.htm

PCA3, THE NEW AND NOVEL PROSTATE CANCER MARKER

Ever since the prostate specific antigen (PSA) was discovered and a test for its urine level developed there has been controversy concerning its utility in providing guidance concerning the risk of prostate cancer and the need for a biopsy. The problem is that PSA is not specific for prostate cancer and can be elevated by such confounding effects as an enlarged prostate or prostatitis. Furthermore, while treatment with 5-alpha-reductase inhibitors (5-ARIs e.g. Proscar, Avodart) lower the PSA level dramatically, corrections for this effect when assessing risk are not precise but thresholds for diagnostic interventions are. Since even men with low PSA levels can have prostate cancer, the only way to be certain is with a biopsy. Lowering the PSA threshold, e.g. from > 4.0 to > 2.5 ng/dL increases the number qualifying as candidates for biopsy. However, even the biopsy is not perfect and can miss a very significant number of positive cancer cases. Furthermore, the biopsy is unpleasant, involves the trans-rectal ultrasound guided sampling of the prostate with, generally, 12 or more hollow needles, and there is the risk of infection, urine in semen or urine, rectal bleeding, urinary retention and even hospitalization, with risks running from 13% to near zero for this list. Thus the dilemma for the clinician and patient since even an abnormal or suspicious digital rectal examination is not a good indicator of the presence cancer, although either an elevated PSA or abnormal DRE or both will frequently lead to a biopsy being suggested.

One option is to calculate the risk of biopsy-detectable prostate cancer using selected risk factors. This generally starts with race, age, PSA level, family history of prostate cancer, the results of the DRE and prior biopsy results if relevant. Then the urologist can add body mass index, use of 5-ARIs and % free PSA.[1] But a major weakness of this approach is PSA, and there is an acute need for a better marker.

A new marker has in fact been discovered, developed and commercialized.[2-4] It is called PCA3, a gene that expresses a non-coding messenger RNA. It is only expressed in human prostate tissue and is highly overexpressed in prostate cancer. This makes it a useful tumor marker and prompted the development of a sensitive assay followed by its commercialization. In mid-February, 2012, the FDA approved the *Progensa*® PCA3 test developed by Gen-Probe. While various versions of PCA3 tests have been available for some time and used in research, this FDA decision will allow Gen-Probe to promote and market their assay. The approval is for use in cases where there is evidence of risk in the presence of a negative biopsy result with the goal of avoiding unnecessary biopsies. The PCA3 test uses a sample of first passed urine after a standardized prostate massage. This is a disadvantage, and urine obtained by a catheter without massage has been tried as well as simply a urine sample. The best results are obtained with the prostate massage technique, as indicated by the yield of samples having measurable amounts of PCA3 mRNA and in addition, enough PSA RNA which is used to form a ratio needed to calculate the PCA3 Score.[4]

FUNDAMENTAL PROBLEM WITH PROSTATE CANCER DETECTION TESTS

First, the patient must deal with probabilities. A 60 year old Caucasian man with a PSA of 1.0 ng/dL, no family history of PC, a normal DRE and no prior biopsy has, according to one online calculator, a risk of 14% for a positive biopsy result. For a PSA of 2.0 ng/dL it is 23%.[1] Making the parameters more unfavourable will dramatically increase this risk. Some patients have never thought about their tolerance for risk presented this way. Some men end up weighing probabilities for finding PC against probabilities for adverse effects of the biopsy. The latter of course present a much smaller risk than PC of morbidity and mortality. Setting a PSA threshold where there should be significant concern is clearly arbitrary. With a low enough threshold for unacceptable risk, practically everyone, especially older individuals would pass the test for needing a biopsy—clearly an absurd situation.

Over the years, the above state of affairs has prompted considerable research directed at a better risk assessment protocol, better adjustment for age, a better marker, a better combination of parameters, etc. But the end result will always be a probability. One is trying to predict what is in the black box without opening it or invasively probing it. The consensus in the urology community seems

to be that anything that increases the predictive power of the pre-biopsy risk assessment protocol is worthwhile. This is probably realistic.

The issues which have guided research on PCA3 involve the use of the test to improve predictions of the biopsy outcome. As well, there is interest in predicting the final picture that emerges after a radical prostatectomy where a detained pathological assessment is compared with clinical observations of the biopsy in connection with the nature and extent of the disease. In addition, the value of the test in the context of active surveillance is of great interest. Finally there is the approved use, i.e. providing guidance regarding if and when to do a second biopsy when the first is negative but there is evidence that cancer may indeed be present.

In studies of the type with which we are concerned here, the statistical presentation is generally in terms of sensitivity, specificity, the negative predictive values, positive predictive values and the so called c-statistic which is the area under a graph (AUC) of sensitivity vs. (1- specificity). If readers want more than a simple statement that a study found the PCA3 test superior, then it is necessary to consider the numerical evidence. While this is really biostatistics 101, it is a bit complicated and one must be very careful with the terminology.

The statistical method identifies *positives* and *negatives*, terms which apply to the PCA3 test result being on one side or the other of the cut-off in the PCA3 Score. The terms *true* and *false* refer to agreement or disagreement between the prediction of the marker at a given cut-off and the outcome of the determination of the presence or absence of the disorder. Biopsies are relied upon to provide the answer. There are now only four possibilities.

- True positive (TP). Urine test positive. PC found on biopsy
- False positive (FP) Urine test positive. No PC found on biopsy
- True negative (TN) Urine test negative. No PC found on biopsy
- False negative (FN) Urine test negative. PC found biopsy

Sensitivity is calculated from the number with a positive urine test who turned out to have PC compared to the total number who were found to have cancer, i.e. TP/(TP + FN). *Specificity* is calculated from the number with a negative urine test who in fact did not have cancer compared to the total number who did not have cancer, i.e. TN/(TN + FP). Another parameter is also important, the *negative predictive value* (NPV). This is the number correctly identified as not having PC compared to the total who tested negative in the urine test, i.e. TN/(TN + FN). Also, the *positive predictive value* (PPV) is the number correctly identified as having PC relative to the total having a positive urine test. i.e. TP/(TP + FP). These four parameters are at the heart of judging screening tests. These are probabilities, generally expressed as percentages by multiplying by 100, and involve averages over the study population. Thus, a sensitivity of 90% means a 90% probability of identifying with the urine test cut-off those who actually have PC. Specificity is the probability of correctly identifying those without PC among the subjects who do not have PC.

The principal goal addressed by the new PCA3 test is unnecessary biopsies, which translates into performing biopsies on individuals with a low probability of having cancer that are viewed as having a high probability. The concept is to have a system, an algorithm or a nomogram which allows the classification of candidates for screening or individuals with suspicious negative biopsy results into two groups on the basis of probabilities and then decide biopsy or no biopsy or delay the biopsy. Unfortunately, these decision or recommendation systems are imperfect, and some of those classified as not needing a biopsy or rebiopsy will indeed have cancer, in some cases dangerous and aggressive. However, most but not all found to have cancer on biopsy really do have the disease.

As mentioned above, the results of the biopsy determine the presence or absence of cancer. In the studies in question used to calculate various probabilities, there is no middle ground or grey area. However, the pathological analysis of biopsy cores requires some judgment and considerable expertise. There will be grey areas associated with cancer vs. pre-cancer. At the low end of the Gleason scoring system there is wiggle room and yet the studies require a yes or no answer, not

maybe. The gold standard is in fact the pathological examination of the prostate after surgery, obviously not a solution to the problem of being sure about the presence of cancer in the context of this discussion, although the results when compared to the marker or markers are of course of great interest.

Biopsies are highly variable procedures. The operator must decide on and hit the regions targeted to sample, and how many samples to take. At one extreme is the saturation biopsy, which can involve up to 24 samples. The traditional biopsy obtained 6 samples, but more modern procedures typically take 12. There can be little doubt that if some patients in a group classified as negative had received a more aggressive biopsy, not all would have been pronounced negative. Studies of multiple repeat biopsies have revealed that each successive one turns up some positives. It is quite amazing that it has been possible to talk a group of men into submitting to as many as 4 rather unpleasant and slightly dangerous procedures and their doctor probably keeps telling them, "I'm almost certain you have PC." One recent study that used a 21 core saturation protocol found that of those negative at first biopsy, 18% had a positive PC diagnosis at second biopsy, and for those still negative, the third yielded 17% and the fourth yielded 14%.[5] Thus even the saturation procedure missed significant numbers of individuals with PC. As applied to testing screening protocols, the gold standard is not exactly pure gold!

The bad news is that all the studies validating the PCA3 test and deriving various statistics measuring of how well the marker performs or allowing comparison with other markers are all based on a test, which is imperfect. In studies it is obviously necessary to identify the patients who are do or do not have PC and they must rely on biopsy results to make the required calculations, but some of the negative cases entered into the equations really do have PC. In the above study with saturation biopsies, of 231 men undergoing the second biopsy, 25 had precancerous conditions at first biopsy (which made them negative for PC) and in this group, 6 cancers were found on repeat biopsy vs. 42 for the total group. Furthermore, when it is calculated that so many biopsies have been avoided by using a given protocol, it should be clear from the above discussion that those enjoying the lack of need for an additional biopsy cannot assume it is certain they are cancer free.

PCA3 AND REPEAT BIOPSY DECISION

First there is the use of PCA3 for guidance in the merits of a repeat biopsy. This situation arises when the urologist considers it highly probable that a negative biopsy is incorrect. The question of a repeat biopsy also comes up when a patient diagnosed with low-risk PC based on biopsy results elects active surveillance and a later repeat biopsy is considered important either when the clinical picture changes or it is part of the protocol to reassure both the patient and his physician concerning the probability that active surveillance is still appropriate. In the first instance, the clinician might consider adding PCA3 to strengthen or weaken the case for the presence of PC and possibly avoid an unnecessary repeat biopsy.

The table below lists the statistical results for repeat biopsy studies using the PCA3 Score cut-off as a positive vs. negative test result where the outcome is the biopsy result of PC or no PC. The four probability parameters described above are given as percentages and N is the size of the study cohort.

Author	SEN	SP	PPV	NPV	N	Score
FDA[6]	78	57	34	90	466	>25
Haese[7]	73	51	NA	NA	463	>20
Ibid	47	72	NA	NA	-	>35
Wu[8]	67	64	52	78	103	>25
Ibid	38	77	50	66	-	>35
Ploussard[9]	77	54	28	91	117	>25*

f/t PSA >20%, the free to total serum PSA. NA = not available, SEN = sensitivity, SP = specificity, PPV and NPV are the positive and negative predictive values. Score is the PCA3 Score.

Recall from the definitions above that sensitivity looks just at those with PC and determines the success of picking them out with the PCA3 test. Specificity looks just at those free of PC and looks at the success of picking them out with the test. The negative predictive value looks at all those with a negative PCA3 test and indicates the percentages that were correctly identified as not having PC. When an increasing diagnostic parameter predicts an increasing probability of having the disorder, then moving up the cut-off decreases the sensitivity but increases the specificity, a sort of can't win situation.

The NPV is quite high with two of three studies giving values ≥ 90%. Put another way, only 10% men relying just on the PCA3 test to decide on a second biopsy would have made a mistake. This is an argument for using the PCA3 test to prevent unnecessary biopsies. But some of the other numbers are not exactly sensational. The positive predictive values are poor, which translates into a low probability that a positive value of the marker, e.g. > 25, leads to finding PC at biopsy among those testing positive with the urine test. Using a PCA3 cut-cut-off as compared to traditional measures such as a PSA cut-off or range, with or without inclusion of free/total PSA %, generally gave a higher predictive accuracy for PC, but the clinical significance of the increase is debatable. When PAC3 was combined with other parameters the predicative accuracy was even better. This has resulted in nomograms[8,10] and internet calculators[1]. See also www.PCA3.org. The bottom line would appear to be that the PCA3 test has many of the problems of the PSA test, only they are not as great and until a better test is found, this is where it's at. An essential feature of both PSA and PCA3 is that they are present in the absence of cancer, and while PCA3 has a number of advantages, this problem remains.

PCA3 AND INITIAL BIOPSY DECISION

Elevated PSA, with or without an abnormal DRE, is central to the decision regarding an initial biopsy. Some physicians will use a nomogram or online risk calculator including PSA and other factors. However, the probability of having PC continuously increases with increasing PSA and even men with low PSA levels can have PC. Thus where to set a cut-off is constantly debated, as is the more general question regarding even using PSA in this context since it is really a highly unsatisfactory indicator.[11] When it is suggested to a man that he should have a PSA test, this is really screening and the issues of overdiagnosis and overtreatment arise if the test is done. PCA3 has the significant advantage as compared to PSA of being much more PC specific, independent of age, prostate size and PSA level. Importantly, the test has just been shown not to be sensitive to the presence of prostatitis.[12] Thus there are also studies of the use of this marker in the context of deciding on an initial biopsy, an application that is not yet approved by the FDA. The studies relevant to this aspect are thus of interest.

If one restricts attention to studies that used the *Progensa* PCA3 test and did not involve a repeat biopsy, then there appear to be three of note. They present only sensitivity and specificity data (given as a %), frequently at various PCA3 Score cut-off values, and also compare PCA3 with traditional markers, generally using the c-statistic.

Author	SEN	SP	N	Score
Deras[13]	63	61	570	>25
Roobol[14]	84	28	721	>20
Ibid	68	56	-	>35
De la Taille[15]	84	55	516	>20
Ibid	64	76	-	>35

Deras *et al* found that PCA3 had better predictive accuracy (based on AUC data) than PSA and when the two were combined, the result was even better.[13] A similar results was obtained by de la Taillie *et al* who also found f/t PSA % and PSA density each also be inferior to PCA3.[15] When PCA3 was added to a model that included age, DRE results, PSA and prostate volume, the predictive accuracy increased considerably. Roobol *et al* also compared PSA to PAC3 and found the predictive accuracy of PCA3 superior.[14] Judging the real significance of these improvements appears highly subjective.

EXAMPLE

Readers of the *Prostate Monitor* are well aware of the ongoing debate concerning PSA screening in general and the PSA threshold that should trigger the suggestion of a biopsy. On the one hand there is concern over missing curable cancers. But there is also the concern over unnecessary biopsies and surgery or radiation therapy for indolent tumors. This is a complex subject since age, comorbidities, life expectancy should enter into the biopsy decision. The following table calculated online at the University of Texas Health Science Center website calculator is of interest.[5] This table applies to a 60 year old with a normal DRE, no family history of PC, and no previous biopsy. PCA3 Scores and PSA are values, not cut-offs.

PCA3 Score	PSA	Risk of Finding PC
-	1.0	14%
	2.0	23%
	3.0	30%
	4.0	35%
10	1.0	9%
	2.0	15%
	3.0	21%
	4.0	25%
26	1.0	15%
	2.0	25%
	3.0	31%
	4.0	39%
50	1.0	21%
	2.0	35%
	3.0	44%
	4.0	50%

The table illustrates the impact of knowing the PCA3 and its magnitude on the calculated risk of PC. The PCA3 Score of 26, which puts one in the ≥ 25 category used in many studies as cut-off for sorting patients with positive vs. negative values of this marker, is also of interest in comparison with the rest of the table. The table also illustrates the statement made above suggesting that patients are confronted with probabilities to which they must relate to take part in the decision process. For example, someone has a PSA of 4.0 and is looking at a risk of 35% for having a positive biopsy. He now gets a PCA3 test and receives a score of 10. Now his predicted risk is reduced to 25%. What to do? The individual is only 60 and has no other PC risk factors. Life is rarely simple and the predictions are merely averages!

Perhaps the most important take-home message is that if one depends on just a PSA and DRE, there is compelling evidence that they are not very reliable. Prostatitis and BPH (an enlarged prostate) can cause elevated values that are not an indication of PC. PCA3 has a significant advantage in that it is independent of prostate volume and BPH, PSA levels, presence of prostatitis, and even outperforms PSA in men treated for BPH with dutasteride (Avodart) with no adjustment in the PCA3 Score needed when comparing the treated and placebo arms.[16] For some, a very low or very high probability generated by either the PCA3 Score or a risk calculated taking into account this and the traditional

risk factors may be make a decision easy, but most are confronted with numbers in the proverbial grey area like the example just given.

For readers who wish to explore in more detail just how the raw clinical data is converted into the statistical framework and results, the details are presented in an appendix to this issue. It uses data from the study included in the FDA report. The appendix can be found at www.yourhealthbase.com/prostate/PCA3appendix.pdf

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