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UNINFORMED CONSENT: MASS SCREENING FOR PROSTATE CANCER

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ABSTRACT
While medicine may agree in principle that cancer screening requires informed consent, such consent is not, in fact, common practice. In the case of prostate-cancer screening this means that men in large numbers undergo PSA testing with little understanding of its liabilities – in particular, that it may or may not decrease mortality, often detects cancer of questionable significance, and may lead to unnecessary surgery. Given that prostate cancer is known to be overtreated and that family history is a risk factor, it follows that a man diagnosed with prostate cancer, even if it is of no clinical significance, automatically promotes his son into the high-risk category; and given that those so categorized are subject to heightened medical surveillance and that the more diligently medicine searches for prostate cancer the more likely it is to find it, it follows that the sons of men diagnosed as a result of PSA testing are at risk of being overdiagnosed (and overtreated) precisely because their father was. Twenty years into the PSA revolution, its generational consequences have not been discussed in the medical literature.

No one would deny that a man undergoing surgery for prostate cancer has a right to informed consent. So too, however, does a man being screened for that disease have a right to be informed of the known liabilities of the screening test itself – in particular, that it may or may not decrease mortality, often detects cancer of questionable significance, and may lead to unnecessary surgery. Yet 'in screening . . . informed choice is not common practice'.[1] In the United States, where prostate cancer 'awareness' has been vigorously promoted, it is thought that a majority of men over age 50 have been screened for the disease. Yet even as American medicine debates the merits of mass screening for prostate cancer, the New Yorker or San Franciscan screened today may have as little idea of what he is getting into as his counterpart twenty years ago who heard only that 'early detection saves lives'. A generation into the era of prostate cancer screening it can be said that the foreseen harms of screening, as well as harms little considered when the era began, have been realized. This American experiment in prevention – and participants in an experiment certainly need to know that they are just that[2] – illustrates the sort of risks that may complicate the search for cancer in its pre-malignant stage, when it is most curable. While other societies, among them Britain, screen less aggressively, they may nevertheless find the American example instructive.

Before the advent of PSA (prostate-specific antigen) testing in the later 1980s, prostate cancer usually went undetected until it manifested itself, at which point, in many cases, it was already too late. PSA enables detection of the disease before it presents any symptom and before it can be discovered by means of the digital rectal exam – at the most medically favorable stage. On this fact rests the value of PSA testing, despite the harms which all, even its defenders, concede flow from it.

[1] A. Barratt et al. Use of Decision Aids to Support Informed Choices about Screening. *BMJ* 2004; 329: 507.

[2] K. Marshall. Prevention. How Much Harm? How Much Benefit? The Ethics of Informed Consent for Preventive Screening Programs. *Can Med Assoc J* 1996; 155: 382: 'Programs of this nature are experimental, and the appropriate ethical norms for obtaining informed consent should therefore apply'.

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Screening a presumptively healthy population for a disease whose biology is poorly understood is an inherently risky undertaking, one of the risks being overdetection. No sooner was screening for prostate cancer launched in the United States than the disease began to be detected at a rate beyond anything in the history of medical statistics.[3] From 1990 to 1991 alone, reported incidence rose 25%.[4] By one recent estimate, as many as 1.3 million American men have been diagnosed with prostate cancer as a result of screening, of whom one million underwent treatment with its adverse effects, with many men being treated for each life presumed spared by early detection[5] – this while prostate-cancer mortality runs at about 3% of the American male population. The disease is being discovered and treated at so disproportional a rate that some physicians now refer, with or without irony, to the 'risk of diagnosis' rather than the risk of prostate cancer as such.

Participants in the landmark Prostate Cancer Prevention Trial (PCPT), which ran from 1993 to 2003, actually were at increased risk of diagnosis. In this carefully designed randomized clinical trial, finasteride – a drug prescribed for enlargement of the prostate – was administered to the treatment group to determine if, as theorized, it cut the incidence of prostate cancer. Subjects underwent regular screening over the term of the study, biopsies if indicated, and, with their consent, a research biopsy at the study's end. Among other notable results, the PCPT demonstrated that the hunt for prostate cancer is all too likely to find it. Indeed, the rate of detected disease ran so high in this intensively screened population – originally classified as low-risk – that even the suppressing effect of finasteride was not quite enough to bring it down to the 'normal' *lifetime* risk of 17%. (And this even though most biopsies in the PCPT took only six cores, as against the ten or twelve that would be taken today.) Clearly, much of this detected cancer might never have come to light but for medical investigation. Contrary to popular belief, not all cancer is destined to be lethal; some, even much may be 'clinically insignificant' – in effect, dormant. Although there is no way to distinguish reliably in any given case between prostate cancer that can be left to itself and prostate cancer that will become aggressive (which greatly complicates prevention), all parties in the medical literature acknowledge that much of the disease detected not only in the PCPT but in the United States at large is indeed unlikely ever to threaten health. Tellingly, one of the arguments being advanced in favor of the chemopreventive use of finasteride, despite its circumstantial association with high-grade cancer in the PCPT, is that by cutting the incidence of prostate cancer it mitigates the harms of overdetection.[6]

If at the beginning of the PSA era American urologists recommended PSA testing despite the foreseen risk that it would engender a sort of artificial epidemic of detected cancer, it was because they assumed that early detection could not but reduce prostate-cancer mortality. In the face of a disease that claimed some 40,000 lives per year in the United States they chose not to wait for the results of randomized clinical trials of PSA's mortality benefit. Of the tens of millions of American men tested between, say, 1989 and 2009, perhaps not many understood that PSA testing was of unproven value and that it leads to overdiagnosis on a large scale – two facts emphasized in the medical literature but, for the general public, drowned out by the message that screening saves lives.[7] Now, with the mixed but in any case sobering results of two RCTs of PSA at last on the record, some conclude that PSA testing has no effect on mortality, some credit the decline in prostate-cancer mortality in the United States to PSA testing in combination with improved treatments, while others point to the incongruity of screening as many as 1400 men, and treating 48, to avert one death.[8] At this point, to give informed consent for PSA testing is to opt for the test knowing that one is considerably more likely to undergo unnecessary surgery with its adverse effects, among them the possibility of impotence, than to benefit from early detection.[9] The evidence strongly suggests that well-informed men are less likely to elect PSA testing.[10]

[3] I. Thompson, M. Resnick & E. Klein. 2001. *Prostate Cancer Screening*. Totowa, NJ: Humana Press: v.

[4] F. Gilliland, W. Hunt & C. Key. Improving Survival for Patients with Prostate Cancer Diagnosed in the Prostate-Specific Antigen Era. *Urology* 1996; 48: 67.

[5] H.G. Welch & P. Albertsen. Prostate Cancer Diagnosis and Treatment After the Introduction of Prostate-Specific Antigen Screening. *J Natl Cancer Inst* 2009; 101: 1325–1329.

[6] 'Given that the likelihood of being diagnosed with [prostate cancer] is directly related to the rigor with which one looks for it, men who are regularly screened have the most to gain from finasteride in terms of a known health-outcome benefit: a reduced likelihood of being diagnosed with prostate cancer and, consequently, being treated for the disease'. H. Parnes et al. Prevention of Hormone-Related Cancers: Prostate Cancer. *J Clin Oncol* 2005; 23: 374.

[7] On the popular belief that screening reduces prostate cancer mortality, see R. Hoffman et al. Prostate Cancer Screening Decisions. *Arch Intern Med* 2009; 169: 1611–1618.

[8] The RCTs are reported in G. Andriole et al. Mortality Results from a Randomized Prostate-Cancer Screening Trial. *NEJM* 2009; 360: 1310–1319 and F. Schröder et al. Screening and Prostate-Cancer Mortality in a Randomized European Study. *NEJM* 2009; 360: 1320–1328. The latter study is the source of the 1400/48/1 statistic.

[9] The US Preventive Services Task Force judges the benefits of prostate cancer screening uncertain but the harms it leads to undeniable. See Screening for Prostate Cancer: US. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2008; 149: 185–191.

[10] Hoffman et al., *op. cit.* note 7.

What of the man having blood drawn for PSA who hears only of the importance of early detection and is unaware of the harms that flow from screening itself? This man may lack information, but his assumption that screening should prevent ills and not cause them deserves respect. The American public would not have gone along with PSA if it had been told by the test's advocates twenty years ago, 'So what if untold thousands of men stand to have unnecessary surgery or radiation, as long as cancer is detected in others at an earlier, more curable stage'. If such an argument had been made, the PSA revolution would have died at birth.

When a screening program is put into place, the public does not expect substantial harm to multitudes of people to ensue from screening itself. However naïve this view may now seem, it finds support in the principles of screening as classically stated forty years ago in a publication by the World Health Organization – principles that merit quoting in full.

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition . . . should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding . . . should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a 'once and for all' project.[11]

In that the natural history of prostate cancer remains obscure to this day, screening for the disease runs afoul of principle seven. And it is the detection of questionably significant (and ill understood) cancer across the population of screened men that has opened the gates to overtreatment with its adverse effects. But note that the WHO principles say nothing about offsetting the harms of screening with benefits. They do not speak of harms at all, evidently because it would be perverse for a test designed for an entire population (principle six) to harm in the name of prevention. It is worth remembering this, if only because the WHO warning of the pitfalls of screening has proved uncannily accurate in the case of PSA: 'The central idea of early disease detection is essentially simple. However, the path to its successful achievement (on the one hand, bringing to treatment those with previously undetected disease and, on the other, avoiding harm to those persons not in need of treatment) is far from simple though sometimes it may appear deceptively easy' (p. 26).

Concerned to avoid harm, the authors of the WHO document advise that 'in enthusiastically attacking disease at an early stage the Hippocratic principle of *primum non nocere* [first do no harm] should not be neglected' (p. 33). The same Latin phrase figures in a trenchant analysis of the PSA problem published in 2007.[12] While attempting to balance the benefits and harms of PSA even though the former remain uncertain while the latter are undeniable (making the two incommensurate), we do well to keep the Hippocratic maxim in mind. Among the disturbing consequences of the PSA revolution is a precedent for causing serious harms to large numbers – violating nonmaleficence – in the interest of prevention. The full implications of the harms to which ill-informed men have subjected themselves during the PSA era are now becoming manifest.

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While conceding that 'it is still not clear that prostate cancer screening results in more benefit than harm', the American Urological Association's 2009 Best Practice Statement on PSA nevertheless recommends screening for many men provided they are 'informed of the risks and benefits of testing before it is undertaken'. But only because PSA testing has been in violation of the bioethical principle of informed consent has it become necessary, some twenty years into the PSA era, for the AUA to remind urologists to inform men of its risks as well as benefits. The balance of PSA's risks and benefits is just what the US Preventive Services Task Force finds indeterminable (owing to the uncertainty of the latter), and the liabilities of PSA are perhaps even more troubling than generally acknowledged.

Among the circumstances to be borne in mind by the man considering PSA testing are his age and risk factors, and of the latter only two are known: prostate cancer in a first-degree relative and African American race. Here I am concerned solely with family history. Like the research from which it derives, the AUA guideline notes both that (a) a father with prostate cancer raises a son's risk of the disease significantly and (b) PSA testing leads to overdiagnosis. Putting (a) and (b) together, we arrive at the inescapable conclusion that *men who opt for PSA testing not only incur the risk of overdiagnosis but, if they are so diagnosed, place their son*

[11] J. Wilson & G. Jungner. 1968. *Principles and Practice of Screening for Disease*. Geneva: World Health Organization: 26–27.

[12] N. Sharifi & B. Kramer. Screening for Prostate Cancer: Current Status and Future Prospects. *Am J Med* 2007; 120: 743–745.

automatically in the high-risk category, with the likelihood of still more pointless treatment. Moreover, most experts would advise the son as a member of a high-risk group to begin screening perhaps ten years earlier than his contemporaries – at age 40. Assuming, then, that a man screened in 1990 had a son aged 20, and that this man was one of the many treated for what the medical literature calls 'pseudodisease'[13] during the PSA era, the son is now, in 2010, at the very threshold where he becomes subject to medical surveillance with all that it may entail. When the authors of the AUA guideline – seemingly oblivious to the irony of citing risk of a diagnosis rather than a disease – state that 'family history of prostate cancer confers a higher risk of prostate cancer diagnosis' (p. 29), they consider a man only in relation to his father or brother. The legacy a man leaves his son by being diagnosed with cancer that might or might not mean anything does not figure in their analysis. Little, indeed, has been said about the generational consequences of mass screening – consequences awaiting not only the sons of the PSA revolution but the daughters of many women diagnosed with breast cancer, another condition identified at a premalignant stage by screening. As with prostate cancer, mass screening for breast cancer is known to lead to overdiagnosis and therefore overtreatment, and the diagnosis of a mother constitutes a risk-factor for the daughter, although there is stronger evidence of a mortality benefit from mammography than from PSA. (Hence the national screening program for breast but not prostate cancer in the UK.) It is because consent to PSA testing has been especially ill-informed that I concentrate on it exclusively here.

The generational repercussions of mass screening are suggested in the findings of the PCPT, wherein no less than 24.4% of the placebo group was discovered to have prostate cancer. The sons of all these men will now be classified as at high risk. They will indeed be at a high risk – of being diagnosed. Among those in the treatment group of the PCPT with a positive family history, the rate of detected prostate cancer was 24.5%, and among men in the placebo group, 30.4%.[14] It bears emphasizing that these extraordinary figures do not denote actual biological risk but risk as determined by PCPT's screening regimen. While it is true that the totals represent the findings of research-driven as well as PSA-driven biopsies, they nevertheless suggest just how deep the pool of questionably significant cancer is among those with a positive family history, and how troubling a burden, therefore, screened men stand to leave to their sons.

Family history appears to weigh heavily on the sons of prostate cancer patients. In one study investigating the effect information about the risks and benefits of PSA had on the decision to be screened, the numbers interested in screening declined markedly among the informed – except if they happened to have a family history. The informational script used in the study, after noting the risk of impotence and incontinence following prostate surgery, went on to report that

> the biggest controversy over the PSA blood test is that no one knows whether men are better off having the test done or not. Right now, there is no evidence that having the test done will allow men to lead longer lives or improve their *quality* of life. . . . [Some] doctors believe that PSA testing may actually be harmful, because most men with prostate cancer found by PSA testing would never have developed a problem from it. . . .[15]

That men with a family history showed a decided interest in screening even after hearing this discouraging report, just when the interest of others waned, suggests the power of that history. As commentators on the study have concluded, 'Family history wiped out the effect of the intervention'.[16] Another study found that almost twice as many men with a positive family and personal history *as men with only their own history of cancer* expressed an interest in screening.[17] A decade ago, a paper on family history and prostate cancer weighed the possibility 'that a detection bias might inflate the observed association. In this context, men with a family history of prostate cancer might be more likely to undergo regular screening or seek medical care for early symptoms of prostate cancer and, thus, have their tumors detected earlier than men without a family history'.[18] But what if the family history that so concerns these sons should be an artifact of the screening revolution? Suppose their father was one of the many whose PSA-related diagnosis of prostate cancer represents overdiagnosis. In this case, the concerned son seeks early detection because the father courted the possibility of overdetection in the first place. From screened father to screened son, the search for cancer perpetuates itself and produces risk inflation.

[13] See, e.g. L. Schwartz et al. Enthusiasm for Cancer Screening in the United States. *JAMA* 2004; 291: 71–78.
[14] I. Thompson et al. The Influence of Finasteride on the Development of Prostate Cancer. *NEJM* 2003; 349: 215–224.
[15] A. Wolf et al. The Impact of Informed Consent on Patient Interest in Prostate-Specific Antigen Screening. *Arch Intern Med* 1996; 156: 1335.
[16] M. Litwin & K. Reid. Quality of Life and Health Behavior in Prostate Cancer Screening Populations. In Thompson, Resnick and Klein, *op. cit.* note 3, p. 192.
[17] D. Vranicar-Lapka et al. Oncology Patients' and Their Significant Others' Responses to a Proposed Cancer Prevention/Detection Program. *Cancer Nursing* 1992; 15: 47–53.
[18] J. Cerhan et al. Family History and Prostate Cancer Risk in a Population-Based Cohort of Iowa Men. *Cancer Epidemiology, Biomarkers & Prevention* 1999; 8: 58.

To some the idea of accounting for the impact of one's decision on the next generation may be too archaic ('The deeds of the fathers are visited on the sons'), and the impact itself too conjectural, to figure in a medical decision, but if a family history of prostate cancer is a recognized risk factor, then my taking on the 'risk of diagnosis' by getting screened can well have a bearing on my son – a bearing not speculative or theoretical but direct. What candidate for PSA testing would not be dismayed to learn that by assuming the 'risk of diagnosis' he increases the likelihood that his son too will be diagnosed? For the implications of being classified as at high risk on account of family history are more than semantic. As in the PCPT, 'the likelihood of being diagnosed with [prostate cancer] is directly related to the rigor with which one looks for it',[19] and the son of a man who had prostate cancer is subject to heightened medical surveillance – specifically, earlier testing, lower cutpoints, likelier biopsies, therefore likelier detection of disease (whether significant or not), and everything else that follows from this sorry chain of events.[20] While he is not destined to follow after his father – for he can, after all, decline to be tested – he does stand on an especially slippery slope. But without good information about prostate cancer and PSA testing the son cannot know where he stands. For years, proponents of PSA testing have endorsed informed consent on paper even while such consent is routinely violated in practice, as the medical literature has documented.[21] Given the potentially profound consequences of any decision to be screened, all candidates for PSA testing need good information about its pro's and con's, and no one more urgently than the son in the high-risk category. Although informing him will not relieve his dilemma, it is the least medicine can do.

That the American Urological Association recommends PSA testing for many, even though it cannot say that the test does more good than harm, suggests that it was committed to PSA before overdetection reached its current magnitude and remains committed despite the troubling ambiguity of the evidence as it now stands. Yet there were doubts about PSA from the early days of mass screening. Among many skeptical estimates of PSA and its benefits, a paper published in 1993 recommended that men be 'fully apprised of the potential downstream risks . . . that could be incurred by the screening test and of the lack of definitive evidence that it favorably affects mortality or that resulting treatment improves quality-adjusted survival'. The authors add, 'If large segments of society are encouraged to participate in PSA testing, a net harm, should it occur, may go undetected. If the history of medicine has taught us nothing else, it has taught us that interventions that seem reasonable based on current medical paradigms may ultimately prove to be worthless or even harmful'.[22] With the sons of the first generation of screened men now coming of testing age, we are in a position to see downstream; and it is clear that, despite the obligation of informed consent, men were not fully apprised of PSA's risks, and despite the obligation of nonmaleficence, the foreseen harms of PSA have been realized and are now being passed to the next generation and even compounded – the sons being subject (as stated) to earlier testing, more intensive surveillance, likelier biopsies, and hence likelier detection of pseudodisease, all because defined as at high risk. The possibility that a test of disputed value might tighten its grip on large segments of society – and this precisely because of its flaws – went undetected twenty years ago, and has escaped discussion now that it has materialised.

Earlier I stated that those taking part in an experiment in mass screening need to know they are doing just that. The same point was made in the *Journal of Medical Ethics* toward the beginning of the PSA revolution:

> Population interventions which have as their goal the prevention of coronary heart disease and many cancers should be classified as population experiments and the same guidelines should apply to them as to clinical trials. That such interventions *are* of an experimental nature and of uncertain benefit is made clear by the fact that they are often tested in randomised controlled trials.
>
> If a healthy volunteer, or a patient, has a right to be fully informed about the risks and benefits of the trial in which he takes part, even more meticulous attention should be paid to the rights of a whole population of healthy people who are subjected to mass prevention programmes and interventions, however well meant.[23]

If American medicine is to begin to extricate itself from the PSA dilemma, it will be by honoring the 'right to be

[19] Parnes et al., *op. cit.*, note 6.

[20] Moreover, some now recommend that men at 'at risk' of prostate cancer consider taking finasteride – even though the circumstantial association between finasteride and high-grade cancer in the PCPT has not been conclusively cleared up. Inflated baseline risk justifies further risk. See J. Xu et al. Estimation of Absolute Risk for Prostate Cancer Using Genetic Markers and Family History. *Prostate* 2009; 69: 1565–1572.

[21] See, e.g. E. DeAntoni. Eight Years of 'Prostate Cancer Awareness Week': Lessons in Screening and Early Detection. *Cancer* 1997; 80: 1845–1851 and G. Gigerenzer et al. Public Knowledge of Benefits and Breast and Prostate Cancer Screening in Europe. *J Natl Cancer I* 2009; 101: 1216–1220.

[22] B. Kramer et al. Prostate Cancer Screening: What We Know and What We Need to Know. *Ann Intern Med* 1993; 119: 919, 921.

[23] P. Skrabanek. Why is Preventive Medicine Exempted from Ethical Constraints? *J Med Ethics* 1990; 16: 189.

fully informed' – that is, by actually providing men with good information about the merits and demerits of PSA. The principle that screening requires informed consent has been affirmed both in the U.S. and the UK, where evidence in favor of PSA has been deemed insufficient to justify national screening. In 2000 the National Screening Committee for the UK concluded that the purpose of information offered to the public about screening should be 'to allow individuals to make informed choices about whether to participate', not simply to encourage participation.[24] Similar views appear to be gaining ground in the United States. The rub is translating them into practice. Only so, however, can the self-perpetuating trend of the overdiagnosis and overtreatment of prostate cancer be slowed.

[24] A. Raffle & J. Muir Gray. 2007. *Screening: Evidence and Practice*. Oxford: Oxford University Press: 249.

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