Survival, Reproduction, and Functional Efficiency

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The article examines the relationship between a trait's effect on survival and reproduction and the notion of functional efficiency underlying the biostatistical theory of health (BST). BST faces the problem of how to measure a trait's joint effect on survival and reproduction in its account of function. If one measures the joint effect by means of the biological notion of fitness, examples such as the hereditary breast and ovarian cancer syndrome do not count as a disorder. If one does not invoke biological fitness, it is unclear how to measure the joint effect while keeping to BST's naturalist credentials.

1. Introduction. The biostatistical theory of health (BST) proposed by Christopher Boorse is widely held to provide the most promising naturalistic account of health and disease. According to BST, a pathological condition is a state of statistically species-subnormal biological part-functional ability, relative to sex and age. More specifically, Boorse (1977, 562) offers the following account of health and disease:

1. The *reference class* is a natural class of organisms of uniform functional design; specifically, an age group of a sex of a species.
2. A *normal function* of a part or process within members of the reference class is a statistically typical contribution by it to their individual survival and reproduction.
3. *Health* in a member of the reference class is *normal functional ability*: the readiness of each internal part to perform all its normal functions on typical occasions with at least typical efficiency.
4. A *disease* is a type of internal state that impairs health, that is, reduces one or more functional abilities below typical efficiency.

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While the core of BST has remained unchanged since it first entered the philosophical debate in the late 1970s, Boorse has modified some aspects of his account in recent years. For instance, the term 'pathological condition' has replaced the term 'disease' in recent statements of the theory (Boorse 2014). More importantly, Boorse (2014) has changed the phrase "survival and reproduction" figuring in the definition of a normal function into "survival or reproduction." This is not a mere terminological issue since the notion of functional efficiency plays a central role in distinguishing between pathological and healthy states. Schwartz (2007), however, points to a potential problem with Boorse's revised account of function. Schwartz suggests that the revised notion is too permissive since it assigns the function of extending survival to a trait that extends survival slightly by interfering with successful reproduction. Boorse (2014, n. 4) acknowledges the theoretical possibility of such a trait but plays down its practical importance.

In this article I take a closer look at the relationship between survival, reproduction, and health. In particular, I introduce a genetic disorder associated with breast and ovarian cancer and discuss its implications for the notion of functional efficiency invoked in BST. Section 2 introduces the hereditary breast and ovarian cancer syndrome as an example in which a genetic trait has opposing effects on survival and reproduction. Section 3 explores the use of the biological concept of fitness for spelling out the notion of functional efficiency in BST. Section 4 considers an alternative joint measure of survival and reproduction. Section 5 discusses the option of modifying the benchmark environment when assessing functional efficiency in BST. Section 6 concludes.

2. HBOC Syndrome. The two major breast cancer susceptibility genes BRCA1 and BRCA2 play an important role in DNA repair and transcriptional regulation in response to DNA damage (Roy, Chun, and Powell 2012). If one copy of either gene is mutated in the germ line, the result is referred to as hereditary breast and ovarian cancer (HBOC) syndrome. HBOC syndrome is associated with not only early onset breast cancer but also an increased risk of ovarian, pancreatic, stomach, laryngeal, and prostate cancer. Importantly, this syndrome accounts for 5%–7% of all cases of breast cancer. Individuals with HBOC syndrome have a lifetime risk of developing breast cancer of 50%–80% compared to an estimated 12% in the total population. For ovarian cancer, the lifetime risk increases from an estimated 1%–2% in the total population to 30%–50% for individuals with HBOC syndrome (Foulkes 2008).

While mutations in BRCA genes have a detrimental effect on the chances of survival, a recent study shows that these mutations increase female fertility by nearly 50%. Smith et al. (2012) analyze the Utah Population Database, which identifies putative carriers of BRCA mutations on the basis of

direct testing of descendants. They show that carriers born before 1930, who would not have used modern contraceptives in their midthirties and who lived until age 45, thereby completing their reproductive period, had nearly two more children than age-matched controls. For women born during 1930–74, carriers had 0.61 more children than controls, the smaller but still statistically significant difference being presumably due to modern methods of birth control. The increased fertility of carriers was due to shorter birth intervals and a longer reproductive tenure.

HBOC syndrome seems to be the kind of trait that Schwartz (2007) has in mind, when discussing the possibility of a trait with opposite effects on survival and reproduction. Given that BRCA mutations increase the ability to reproduce at the cost of the ability to survive, one can attribute the function of enhancing reproduction to these genetic variations. In Schwartz's view this approach yields an overly liberal notion of function at the core of BST.[1]

3. Fitness. Examples of conditions such as HBOC syndrome suggest introducing a 'common currency' that allows weighing the potentially opposing effects on survival and reproduction in order to assess whether there is a net improvement or decline in functional efficiency.[2] A natural candidate for this currency is provided by the biological concept of fitness. Indeed, Hausman (2012, 521) suggests that "without reference to fitness there may be no way to judge whether there has been a net improvement or decline in functioning." Before doing so, however, some objections against the use of fitness in BST have to be dealt with.

Boorse (1977) makes it clear that the biological concept of (Darwinian) fitness is not suitable for cashing out definition 2 in BST. Boorse writes: "The notion cannot, however, be 'Darwinian fitness,' or pure reproductive success. Parents hardly become healthier with each successive child, nor would anyone maintain that the healthiest traits are the ones that promote large families" (548). Similarly, Hausman (2015) takes a critical stance when it comes to the idea of using the concept of fitness in order to develop the notion of functional efficiency in his account of health. "The consequence

1. To be precise, Schwartz contemplates a trait that enhances survival at the cost of reproduction. BRCA mutations have the opposite effect.

2. In response to Schwartz's suggestion that a trait that enhances survival at the cost of reproduction (or vice versa) might be considered as having the function to do so, Boorse (2014, n. 4) suggests that this could only be true of an individual but hardly part of a normal species polymorphism. A normal species polymorphism consists of normal variants, that is, variants of equal functional capacity (699). Clearly, BRCA mutations are too frequent to be dismissed as singular oddities. But what about the idea that these mutations do not have equal functional capacity? Again, what is needed is a common currency comparing the effects on survival and reproduction.

in terms of which a scalar comparison of health might be defined is not reproductive success, because a healthier animal need not (on average) be more successful at reproducing, and an animal with traits that diminish fitness is not thereby unhealthy. . . . A fertile eagle that flies clumsily and slowly is less healthy even though it is fitter than a well-coordinated infertile eagle" (30).

To begin with, it is important to note that the actual reproductive success of an organism is typically not the quantity of interest when assessing its fitness. Rather, fitness is measured by means of the expected reproductive success, that is, a mathematical quantity averaging over possible reproductive scenarios weighted by their probability. As such, fitness describes the disposition of an organism (or a trait) to reproduce. On the basis of this measure, trait *A* can be ascribed a higher fitness than trait *B*, even though a particular carrier of *A* has fewer offspring than a particular carrier of *B*. It is therefore wrong to say that invoking fitness in an account of functional efficiency commits one to the view that an organism is getting healthier with each successive child.[3]

Hausman (2015) is more careful in referring to the average number of offspring rather than the actual number of offspring of an organism in his discussion of the potential role of fitness in an account of health. However, he is also skeptical that reproductive success is the right standard for measuring overall functional efficiency in an account of health and argues for the use of survival probabilities for that purpose: "With respect to any specified environment, one might hope that ornithologists can in principle rank each array of efficiencies of part function with respect to their consequences for survival and reproduction (but mainly for survival) and thereby achieve a complete ordering of the health states of eagles. It is far from obvious how to do this. The most promising route is, I conjecture, to focus on survival probabilities for some specified period for average members of relevant reference classes in benchmark environments" (30).

I have two issues with giving priority to survival probabilities rather than measures of expected reproductive success when assessing functional efficiency. First, there is an important asymmetry that makes the expected reproductive success a measure of both reproduction and survival while the survival probabilities merely capture a fact about survival. As already indicated, an organism that does not reach reproductive age cannot reproduce. As such, the expected reproductive success is sensitive to the survival of an

3. Note that this argument differs from a recent response to Boorse's critical view on the concept of fitness in the context of BST. Griffiths and Matthewson (2018) point out that more offspring does not necessarily equate to higher fitness since larger families may have less robust offspring and lower rates of survival to reproductive maturity. While my reply to Boorse builds on the fact that fitness is measured by a mathematical expectation, Griffiths and Matthewson's reply relies on taking into account the costs associated with raising offspring until reproductive maturity.

organism and can be said to measure both facts about survival and reproduction. Now, one can object that the expected reproductive success is only sensitive to survival until the reproductive cycle has been completed and that postmenopausal survival does not matter. This, however, is not necessarily the case. The grandmother effect postulates that the postmenopausal survival observed in human females, as opposed to those of other primates, is selectively advantageous because postmenopausal women may increase the number of their grandchildren by offering support to their daughters and grandchildren (Hawkes et al. 1998). If there is a strong grandmother effect in a population, then postmenopausal survival will have an indirect effect on the number of surviving offspring. In that case, the expected reproductive success can be truly said to be a measure of survival and reproduction.

Second, the preference for survival probabilities over measures of reproductive success threatens to undermine Hausman's writings on a related topic. Since normal human functioning varies among groups, BST requires the choice of a reference class in order to distinguish health from pathology. In particular, Boorse (1977) chooses an age group of a sex of a species for this purpose. Kingma (2007) argues that proponents of BST fail to justify this choice of a reference class. In order to respond to the reference class problem, Hausman (2015, 11) points out that there is a good reason for choosing reference classes in BST on the basis of sex since sexual differentiation is necessary for reproduction, which he considers as one of the highest-level biological goals. Given the importance attributed to reproduction, it is unclear how the choice of a standard for functional efficiency that ignores reproduction can be justified without damaging the justification for the choice of reference classes in BST.

Assuming that we can set aside this common criticism raised against the use of fitness in BST, the question arises of how to measure the fitness of BRCA mutation carriers. To get started, let us return to the study by Smith et al. (2012) on the fertility of BRCA mutations. For women born before 1930, a member of the control group gave, on average, birth to 4.19 children and a carrier gave, on average, birth to 6.22 children. These numbers represent a 48% increase in fertility measured by the number of children ever born. A similar picture arises if one estimates the mean number of children who survived to adulthood. Again, carriers born before 1930 have on average two more children than noncarriers on the basis of this fertility measure.

While the average number of children ever born is employed as a fertility measure by Smith et al. (2012), this measure is also sensitive to the survival chances of carriers and noncarriers since a woman who dies prematurely cannot reproduce. As such, the average number of children ever born can be seen as a fitness measure combining both fertility and mortality. Indeed, the average number of children born approximates the expected lifetime reproductive success, that is, a fitness measure widely employed in life history

theory. Life history theory focuses on the strategic decisions over an organism's lifetime (Roff 1992; Stearns 1992). The theory treats the evolution of life histories as an optimization problem and asks, what are the optimal values of life history traits that maximize reproductive success given particular ecological factors that affect an organism's probabilities of survival and reproduction and given limiting constraints and trade-offs that are intrinsic to the organism?[4]

There is, however, one important caveat in using the fertility data from Smith et al. (2012) to calculate fitness values of patients with HBOC syndrome. Smith et al.'s study also contains a survival restriction, that is, only women who survived to at least age 45 were included in the study. As a consequence, 12% of carriers and 5% of controls were removed from the data set. It seems plausible that the difference in these percentages reflects the difference in risk of developing associated cancers. Making the conservative assumption that these women left no surviving offspring, one can calculate the average number of offspring reaching adulthood. After these adjustments, carriers had 5.13 surviving children, and controls, 3.65 surviving children (da Silva 2012). While this reduces the increase in fitness due to BRCA mutations to 41%, this difference still amounts to a substantive selective advantage of mutation carriers over noncarriers.

Supplementing BST's account of function with the biological notion of fitness as a joint measure of survival and reproduction leads to the conclusion that patients with HBOC syndrome do not have a decreased level of functional efficiency and, hence, do not have a disease on the basis of this account. This assessment sits uneasily with the fact that HBOC is commonly referred as a genetic disorder in the medical literature (e.g., Hunter et al. 2016). Since BST aims to identify pathological conditions in line with medical usage, the assessment of whether HBOC constitutes a disease needs to pay close attention to this view.

Labeling medical conditions that enhance the risk of developing other medical conditions, such as breast cancer or heart disease, as diseases reflects a contemporary trend in 'risk-based medicine'. For instance, obesity is now considered a disease by the American Medical Association (Stoner and Cornwall 2014). This trend, however, has not remained unchallenged in the philosophical literature. A number of philosophers of medicine have argued for keeping risk factors and diseases conceptually distinct (e.g., Schwartz 2008; Boorse 2014). Personally, I am sympathetic to an idea, expressed by Matthewson and Griffiths (2017, 462), according to which it becomes less

4. The general fitness measure used in life history theory is given by the expected number of descendants left far into the future by an organism. In the case of stable populations that do not change in size, this quantity reduces to the expected number of surviving offspring that are produced over a lifetime.

probable that medicine will distinguish between risk factors and diseases in cases in which risk factors have direct and severe implications for the chances of survival or reproduction of an organism. Such a language seems warranted in the case of HBOC syndrome, given that female BRCA mutation carriers have a high lifetime risk of developing breast cancer.

4. Other Joint Measures. Using the idea of applying the biological notion of fitness to the account of function employed by BST, the discussion has focused on the expected lifetime reproductive success as a measure for capturing a trait's joint effect on survival and reproduction. However, nothing prevents the proponent of BST from developing alternative measures for that purpose. For instance, one could use a linear combination of survival probabilities and reproduction probabilities to measure the functional efficiency of a trait. More formally, let us denote the survival probability until, say, age 70 as P_S. Further, let P_R denote the probability that an organism produces at least one viable offspring during its lifetime. Now, a trait's joint effect on survival and reproduction can be measured by the linear combination $\alpha P_S + \beta P_R$, with α and β denoting some positive constants adding up to one.

If one leaves the domain of evolutionary biology behind, it is difficult to see how a particular assignment of weights α and β can be justified without making reference to individual or societal preferences on how to value a human's survival over its reproduction (and vice versa). Take Hausman's suggestion to rank traits "mainly" on the basis of their effect on survival while still taking into account the impact on reproduction (2015, 30). Translating this proposal into the context of using a linear combination of survival and reproduction probabilities seems to suggest choosing a larger numerical value for parameter α than for parameter β. How can this choice be grounded? In evolutionary biology there is a fact of the matter as to whether a fitness measure is the right predictor of evolutionary success given particular model assumptions. For instance, the expected lifetime reproductive success serves as an adequate predictor of a trait's long-term evolutionary success if there are no year-to-year variations in factors such as weather and population density. In the biological context there is a further criterion—here, the population structure as time goes to infinity—that can be used for justifying the choice of one fitness measure over another.[5] No such independent criterion seems to be available to someone arguing that in every application of BST, a trait's impact on survival has to be weighted stronger than the impact on reproduction. As a result, there is a parting of ways between the notion of fitness in

5. I should mention an important caveat. Biologists can be interested in both the short-term and the long-term evolutionary success of a trait. In general, short-term fitness measures differ from long-term fitness measures (Sober 2001). Hence, the choice of a fitness measure depends on the prior selection of a relevant time horizon of interest.

evolutionary biology and attempts to formalize a joint measure of the effects on survival and reproduction in the context of BST.

Naturalist accounts of health assert that whether a part of an organism is functioning adequately is a scientific rather than an evaluative matter (Hausman 2012, 524). The previous discussion suggests that if one drops the commitment to the biological notion of fitness as the joint measure of survival and reproductive success, nonscientific considerations come into play when designing such a joint measure. Hence, by cashing out the difference between health and pathology by reference to the functioning of a part of an organism, BST does not qualify as a naturalist account of health. My comments are, of course, relative to the use of the linear combination of P_S and P_R as a measure for capturing a trait's net effect on survival and reproduction. Nothing follows directly from this assessment for possibility of viable alternative measures. However, measures of this kind are typically not made explicit in the literature on BST. For instance, while Hausman (2015, 30) acknowledges the difficulty of identifying a measure of overall functional efficiency, he only gestures at a possible solution by suggesting the choice of survival probabilities. I take the sparse writing on this issue as an indication that outside the domain of evolutionary biology there is no joint measure of survival and reproduction that satisfies the criterion for a naturalist account of health.

In the previous section I argued that supplementing BST's notion of function with the biological concept of fitness does not account for the view that HBOC syndrome constitutes a disorder. In this section I explored the use of alternative joint measures of survival and reproduction for measuring overall functional efficiency in BST. While these alternative measures might well reproduce the view that HBOC syndrome constitutes a disorder, the justification for these measures seems to violate the naturalist credentials of BST. Where does this leave us with regard to the prospect of developing a naturalist account of health invoking the notion of a trait's functional efficiency? One option is to restrict BST to the domain of traits that do not have conflicting effects on survival and reproduction. In these cases it seems uncontroversial to rank traits on the basis of their functional efficiency. For instance, suppose that carriers of trait *A* have both larger chances for survival until, say, age 60 and higher chances of successful reproduction than carriers of trait *B*. Here, it is difficult to object to the view that trait *A* has a higher functional efficiency than trait *B*. The problem with this proposal, however, is that such a constrained account of health and pathology is unsatisfactory. Cases such as HBOC syndrome are not construed in the philosophical armchair but constitute garden variety medical conditions. A naturalist theory of health and disease should be able to handle them. In the final section I therefore consider a further possible response on how to account for the view that HBOC constitutes a disorder from the perspective of BST.

5. Benchmark Environment. According to Smith et al.'s study on the fertility of women with HBOC syndrome born before 1930, mutation carriers have a strong selective advantage over nonmutation carriers. There is, however, something puzzling about this result. If carriers of BRCA mutations have such a strong fitness advantage, then one might wonder why these mutations are not more frequent in the human population because of the workings of natural selection. This suggests that carriers of BRCA mutations have not, in fact, experienced a strong selective advantage in the recent evolutionary past and that an adequate quantitative fitness assessment has to take into account further aspects about the evolutionary environment. Da Silva (2012) proposes that the 'grandmother effect' combined with limited female fertilities in ancestral hunter-gatherer societies resulted in weak net selection against BRCA mutations, thereby explaining the fact that these mutations are not common in modern populations. Furthermore, women's fertilities in hunter-gatherer societies are severely limited due to a short reproductive tenure and long interbirth intervals, which would reduce the fertility differences between carriers and noncarriers (Pennington 2001).

While comparisons of functional efficiency can be relative to any specific environment, judgments whether parts of an organism are healthy or pathological are relativized to a 'typical' (Boorse 2014) or 'benchmark' environment (Hausman 2012, 2015) in BST. Hausman (2012, 536) defines benchmark environments as environments that are "benign, common and relevant." Similarly, Hausman (2015, 11) understands a benchmark environment as being "typical of the most common environments in which *Homo sapiens* have lived." Hausman uses the example of phenylketonuria (PKU) to illustrate how the notion of a benchmark environment applies to BST. Infants born with PKU develop severe cognitive disabilities when they are fed a normal diet since they are unable to break down phenylalanine, an amino acid that is found in ordinary diets. However, if these children are fed a low-phenylalanine diet, they develop no symptoms. Importantly, there exist environments with different distributions of amino acids in which only those infants with PKU would not develop cognitive disabilities. By considering an environment with phenylalanine rich foods as the benchmark environment, BST classifies PKU as a disorder.

So far it was, at least tacitly, assumed that the benchmark environment needed for applying BST to the case of HBOC syndrome is given by the environment typically faced by modern humans. One might wonder, however, whether BST can account for the dysfunctional character of BRCA mutations by changing the assumed benchmark environment. More specifically, one might suggest that the ancestral environment of hunter-gatherers constitutes the benchmark environment for assessing whether HBOC syndrome is pathological. By doing so, mutations in BRCA genes are dysfunctional since these mutations have a fitness disadvantage compared to the nonmutated

BRCA genes in the ancestral environment. Assuming that the functioning of mutation carriers is significantly reduced below the population mean in ancestral hunter-gather populations, BST then classes HBOC syndrome as a disorder. Note that this is not a trivial assumption, given that BRCA mutations are only weakly selected against in ancestral populations, according to da Silva's analysis. The main problem with this proposal, however, is that adopting the environment faced by hunter-gatherers as the benchmark has some counterintuitive consequences from the perspective of BST. For instance, Schwartz (2008) argues that a number of medical conditions, such as normal blood pressure, that are not considered as pathological by current standards would be deemed pathological, if one adopted traditional hunter-gatherer societies as the relevant reference class. As such, modifying the benchmark environment underlying judgments concerning health and pathology in BST does not seem to be a viable option when assessing whether HBOC syndrome is pathological.

6. Conclusion. In this article I examined the relationship between survival, reproduction, and health in BST. I argued that BST faces two options. Either one measures a trait's joint effect on survival and reproduction by means of the biological notion of fitness or one does not. In the first case, examples such as the BRCA mutations underlying HBOC syndrome do not count as a disorder. In the second case, it is unclear how to measure a trait's joint effect on survival and reproduction while keeping to BST's naturalist credentials. Finally, I explored modifying the benchmark environment assumed in the analysis. I explained that while adopting the ancestral environment of hunter-gatherers vindicates the view that HBOC syndrome counts as a disorder, it also renders a number of other, unproblematic medical conditions, such as normal blood pressure, pathological.

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