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COMMENTARY

Assessing the risks and benefits of diagnosing genetic conditions with variable phenotypes through population screening: Klinefelter syndrome as an example

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Abstract Consideration of postnatal population-based genetic screening programs is becoming increasingly common. Assessing the medical and psychosocial impacts of this can be particularly complex for genetic conditions with variable phenotypes, especially when outcomes may be more related to quality of life rather than reducing physical morbidity and mortality. In this article, we present a framework for assessing these impacts, by comparing diagnosis and non-diagnosis at different age points. We use the example of Klinefelter syndrome, a common yet frequently under-diagnosed genetic condition for which interventions are available. This framework can be used to supplement established screening guidelines and inform decision-making.

Keywords Klinefelter syndrome · Genetic testing · Genetic screening · 47,XXY

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Background

Rapid advances in both our understanding of the genetic contribution to various diseases and in genetic technology have increased the scope for genetic testing. In the past, such testing has usually been performed to elucidate a diagnosis for a symptomatic individual, or to provide a strong prediction of disease risk where effective interventions for prevention, treatment or surveillance exist. However, our expanding genetic knowledge means that a test result may now provide only a spectrum of individual lifetime possibilities, sometimes in a currently asymptomatic individual.

In this context, the opportunity to undertake postnatal, population-based genetic screening for phenotypically variable conditions is becoming more common (Godard et al. 2003). The balance of risks and benefits of diagnosing such a condition in these situations is not always clear, and pressing questions arise as to when it is socially and ethically appropriate to screen. The consequences of diagnosis can be difficult to quantify when clinical presentation is highly variable between individuals. In this setting, the goals of diagnosis through screening shift away from minimising mortality and severe medical consequences, to less tangible outcomes such as decreasing psychological morbidity, preventing less severe medical consequences, and ultimately, towards maximising quality of life (QoL).

Klinefelter syndrome (KS) is one such phenotypically variable, non life-threatening condition, for which population screening could be considered. Using the case of KS, we present here a framework for systematically organising the information needed to address these questions. As such, this article addresses the underlying principles involved in diagnosing such a condition through population screening, as opposed to the technicalities and logistic considerations

of screening for a chromosomal disorder. We believe that this approach will be useful for framing the complexities associated with other genetic or genetically influenced conditions.

Klinefelter syndrome

The following features make the decision to undertake population screening for KS a complex issue, requiring a holistic consideration of both medical and psychosocial impacts:

- *A variable phenotype*, ranging from "near-normal" (or seemingly clinically benign) to significantly affected
- *A strong psychosocial component*, also variable but not usually including intellectual disability
- *Interventions of uncertain benefit*, available from early childhood but for which the effect on later outcomes has not been fully established

KS is a common genetic condition (47XXY) affecting males with an estimated prevalence of 1:660 (Bojesen et al. 2003)—equating to over 640,000 males with KS across Europe. The additional X chromosome results in a spectrum of clinical features ranging from infertility, small testes, testosterone deficiency, breast development, and decreased facial and pubic hair, to varying levels of specific cognitive, social, behavioural and learning difficulties (Simpson et al. 2003). Despite these features, up to 70% of KS remains undiagnosed and of those that are detected, diagnosis is not usually made until later in adulthood (Bojesen et al. 2003). As only the most florid cases tend to be detected by current postnatal surveillance (Abramsky and Chapple 1997), this may lead to the perception that KS is rare and that all patients exhibit a 'classic textbook' phenotype. In actuality, the only consistent finding is small testes (Smyth and Bremner 1998), which often escapes detection highlighting the low prevalence of male genital examinations in routine health care (Handelsman and Liu 2006). In addition to low awareness of the condition amongst health professionals, lack of diagnosis has also been attributed to the sometimes subtle clinical picture and the small fraction of affected men who seek medical attention (Lanfranco et al. 2004).

Since it was first described in 1942 by Dr Harry Klinefelter, early detection of KS has been advocated for, based on the hypothesis that treatment and intervention at the appropriate ages and stages of development would result in better health and QoL outcomes in adulthood, even for individuals presenting at the less severe end of the spectrum. Learning, speech and behavioural therapies are available from early childhood if required (Rovet et al. 1996; Simpson et al. 2003), and the most prevalent intervention for KS is testosterone treatment commencing in puberty, which can have both short- and long-term medical benefits in addition to profound positive psychosocial effects (Nielsen et al. 1988). Therefore, the issues of both late diagnosis and non-diagnosis of KS are regarded as problematic, as these individuals may indeed benefit from available medical, educational and psychosocial interventions.

As KS is not usually obvious in childhood, early detection could only be ensured by population screening. Given its high prevalence, significant under-diagnosis and available treatment options, KS is an ideal candidate for a postnatal, population-based genetic screening program. However, there may be downsides to such a program: ultimately, it remains unknown how 'life is' for the currently undiagnosed majority of individuals with KS, and it may be that early detection would not only fail to improve QoL, but could even cause harm (e.g. by damaging self-esteem, identity formation or parent-child bonding). Given these potential harms and taking into consideration available treatments, it is important to explicitly ask whether screening for KS is ethically and socially appropriate, rather than simply assume that it is.

The framework

This framework is designed to be used as a tool for providing refined information to assess potential individual risks and benefits of diagnosis and non-diagnosis of a particular condition where these are not immediately evident and allows the consideration of multiple inter-related outcomes.

Table 1 shows the steps involved in constructing the framework, which we have applied using KS as an example. This framework elucidates the key issues that need to be resolved in relation to screening for KS.

Identify developmental stages or age points where screening could occur

The initial step in structuring the framework is to determine hypothetical condition-specific age points where implementing population-based screening might be appropriate. For KS, we determined the most suitable points by considering:

- *Logistical factors*—ages and settings where large numbers of the population are together at the same time and place, so that screening is logistically easier to implement, more cost-effective and likely to reach a significant proportion of the target population.
- *Developmental factors*—ages representing significant points in development, both an individual's general development and the development of the condition,

Table 1 Key steps involved in using the framework

Identify developmental stages or age points where screening could occur
Classify the known potential consequences of diagnosis and non-diagnosis at each specified age point
Identify existing information about these consequences and highlight the evidentiary gaps
Conduct (if appropriate) research that aims to fill the evidentiary gaps
Consider and compare the individual consequences of diagnosis and non-diagnosis to inform a decision regarding screening

where specific treatments and interventions become particularly relevant.

Based on these, specific age points were chosen for comparison to the most common scenario of never being diagnosed as shown in Table 2.

Each point has its own unique set of medical, psychosocial, community, social, economic, cultural and ethical factors influencing possible outcomes of diagnosis. Therefore, as the risks and benefits under each point will be weighted differently, they must be analysed individually (e.g. the most logistically suitable screening point may be the least psychosocially beneficial).

Classify the known potential consequences of diagnosis and non-diagnosis at each specified age point

Next is consideration of the different types of medical and psychosocial consequences that could result from diagnosis and non-diagnosis:

- The known natural history of the condition is used to *classify specific subcategories and predict possible consequences* within each. This is achieved by considering significant points in management (e.g. testosterone treatment) in relation to individual general development (e.g. onset of puberty).

Figure 1 demonstrates this method of categorisation, which allows for clear identification of the consequences of *being diagnosed* versus *not being diagnosed*. This is an important distinction because missed past opportunities for treatments and interventions are distinct from missed future opportunities. For example, a benefit of being diagnosed with KS at high school entry is that testosterone treatment can be implemented if and when required, while a risk of NOT being diagnosed at this point is that testosterone treatment will not be implemented if and when required, potentially resulting in testosterone deficiency and the accompanying health consequences. In considering the prospective risks and benefits of not being diagnosed at a particular point, it has been assumed that diagnosis will occur at the next hypothetical screening point.

The psychosocial risks of being diagnosed mirror the psychosocial benefits of not being diagnosed, and so only the consequences of diagnosis need be included in the framework (e.g. a potential risk of being diagnosed is experiencing stigmatisation, whereas a potential benefit of not being diagnosed is not experiencing stigmatisation).

Identify existing information about these consequences and highlight the evidentiary gaps

In the previous step, all known, probable and possible risks and benefits of diagnosis and non-diagnosis were identified from the literature and placed in the framework. Insert article references in each box to both support and supplement each possible consequence:

- *Seek information from condition-specific studies* (e.g. evidence for benefits of testosterone treatment).
- *Seek information from studies of other genetic conditions* similar in regards to

1. screening and diagnosis properties (e.g. newborn screening for cystic fibrosis may impact on parent-child bonding (Grosse et al. 2004)).
2. phenotypic properties (e.g. assistance for specific learning difficulties may improve school performance (Aram and Nation 1980)).

We developed basic categories indicating the *type* of evidence provided by each source of information:

- Direct (pertaining directly to KS),
- Indirect (pertaining to another condition but applicable to KS), or
- Speculative (theoretically possible and probable, given the nature of the condition, but without data to provide direct or indirect evidence).

References are organised according to these categories and listed against each potential risk and benefit in the framework. This process clearly identifies where little or no information exists.

Conduct research (if appropriate) that aims to fill the evidentiary gaps

For conditions where significant evidentiary gaps are identified, it must be decided whether additional information through further research is required before any recommendation for screening can be made. It may not be

Table 2 Hypothetical age points selected for population screening of KS and relevant logistical and developmental factors in determining each point

Screening point	Age	Logistical factors	Developmental factors
Newborn	3 days	Heel prick within 48 h of birth, performed on vast majority of newborns	
Infancy	1 year	Routine health check/vaccination point, performed on approximately 75% of infants	Development of speech, movement and motor skills
Primary school entry	5-6 years	Primary school entry vaccination point	Commencement of formal education and learning
High school entry	11-12 years	High school entry vaccination point	Commencement of puberty
Adult	20 years and older	Included in analysis as arbitrary point for comparative purposes	

essential or possible to conduct the research in the time needed to make a decision. Where further research is required and will be conducted, the framework provides a solid foundation from which a suitable protocol can be designed. In cases where no gaps are identified, the framework simply contributes to the overall process of program consideration.

In regards to KS, the framework clearly identifies a lack of knowledge regarding the psychosocial impact of being diagnosed with and living with the condition. There is also little knowledge of how age at diagnosis impacts on QoL and other outcomes in adulthood.

Consider and compare the individual consequences of diagnosis and non-diagnosis to inform a decision regarding screening

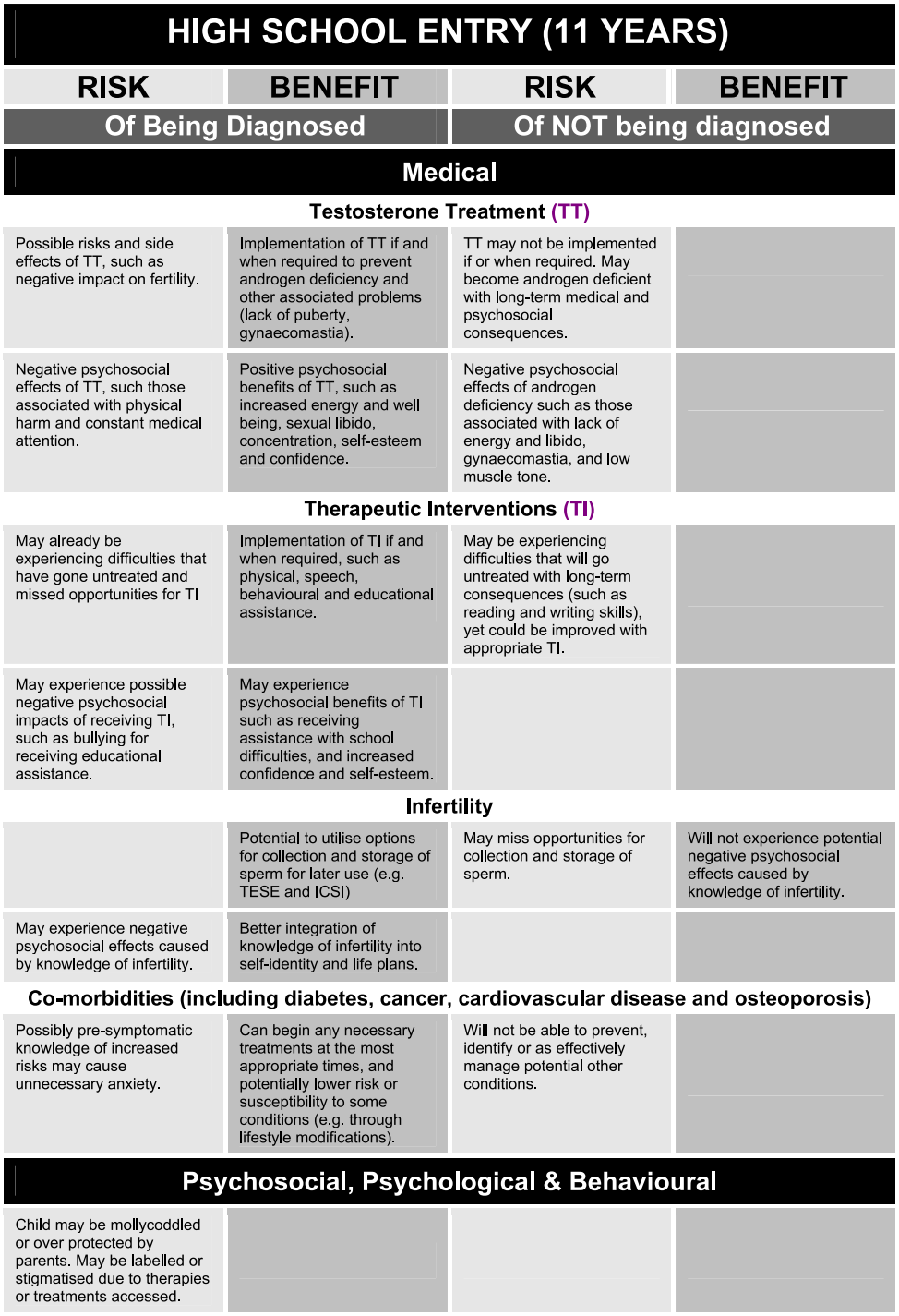
The final step involves weighing up the potential positive and negative consequences of diagnosis or non-diagnosis for individuals at each point, to identify at which one the consequences of being diagnosed are most beneficial overall. In some cases, it may be quite clear where overall advantages outweigh overall disadvantages. However, quantifying risks and benefits that include both medical and psychosocial elements is difficult, even where there is reliable evidence. When considering conditions with highly variable phenotypes, there will inevitably be some degree of uncertainty. To deal with this, a scoring system including a numerical means of weighting each consequence according to probability and magnitude can be incorporated into the framework.

It is also important to allow for future developments in treatment and technology to be incorporated into the framework. In KS, it has been suggested that cryopreservation of sperm or stem germ cells early in puberty and prior to testosterone treatment, may soon be an option (Paduch et al. 2009). This procedure would only be possible if individuals were identified prior to this developmental point. Given that infertility is the most consistent feature of KS, an intervention for this would impact significantly on the overall weighing up of risks and benefits.

Broader applications

Used in conjunction with established screening guidelines and broader evaluation processes (for example, as a tool to assess the clinical utility of a test as part of the ACCE Model Process (Haddow and Palomaki 2003)), the framework can contribute to the assessment of ethical, social, legal and economic issues associated with possible screening programs to determine the most appropriate action regarding the implementation of such programs.

The framework itself does not produce a definitive answer about whether or how screening should be introduced. It is still necessary to decide how much evidence is sufficient for making an informed decision. A complete evidence base is not always available (and may never be); seeking more evidence before a decision regarding the implementation of a genetic screening program costs time and money. In addition, this framework only addresses the individual consequences of diagnosis and non-diagnosis with a particular condition. Whilst this is one important criterion in deciding whether to screen, it is not the only one. Other ethical and public health criteria relate to social goods, including benefit to society at large, economic considerations, and the risk to healthy individuals of false positives. As stated above, existing guidelines have been developed to account for these other factors. The value of this framework is in providing a better assessment of the specific factors which contribute to the overall impact on individuals who are diagnosed as a result of the screening program.



HIGH SCHOOL ENTRY (11 YEARS)			
RISK	BENEFIT	RISK	BENEFIT
Of Being Diagnosed		Of NOT being diagnosed	
Medical			
Testosterone Treatment (TT)			
Possible risks and side effects of TT, such as negative impact on fertility.	Implementation of TT if and when required to prevent androgen deficiency and other associated problems (lack of puberty, gynaecomastia).	TT may not be implemented if or when required. May become androgen deficient with long-term medical and psychosocial consequences.	
Negative psychosocial effects of TT, such those associated with physical harm and constant medical attention.	Positive psychosocial benefits of TT, such as increased energy and well being, sexual libido, concentration, self-esteem and confidence.	Negative psychosocial effects of androgen deficiency such as those associated with lack of energy and libido, gynaecomastia, and low muscle tone.	
Therapeutic Interventions (TI)			
May already be experiencing difficulties that have gone untreated and missed opportunities for TI	Implementation of TI if and when required, such as physical, speech, behavioural and educational assistance.	May be experiencing difficulties that will go untreated with long-term consequences (such as reading and writing skills), yet could be improved with appropriate TI.	
May experience possible negative psychosocial impacts of receiving TI, such as bullying for receiving educational assistance.	May experience psychosocial benefits of TI such as receiving assistance with school difficulties, and increased confidence and self-esteem.		
Infertility			
	Potential to utilise options for collection and storage of sperm for later use (e.g. TESE and ICSI)	May miss opportunities for collection and storage of sperm.	Will not experience potential negative psychosocial effects caused by knowledge of infertility.
May experience negative psychosocial effects caused by knowledge of infertility.	Better integration of knowledge of infertility into self-identity and life plans.		
Co-morbidities (including diabetes, cancer, cardiovascular disease and osteoporosis)			
Possibly pre-symptomatic knowledge of increased risks may cause unnecessary anxiety.	Can begin any necessary treatments at the most appropriate times, and potentially lower risk or susceptibility to some conditions (e.g. through lifestyle modifications).	Will not be able to prevent, identify or as effectively manage potential other conditions.	
Psychosocial, Psychological & Behavioural			
Child may be mollycoddled or over protected by parents. May be labelled or stigmatised due to therapies or treatments accessed.			

Fig. 1 Structure of the framework using categories and subcategories, as described in Step 2. Step 3 involves inserting article references which show evidence for each potential consequence, and then grouping the type of evidence provided by each reference. This box is repeated for each potential screening point selected

Conclusion

This framework has a user-friendly structure, providing a systematic assessment of available evidence for one aspect of the consequences of screening, and a clear method of visualisation. For genetic conditions such as KS which do not fit a traditional disease model, the assessment of potential consequences within this structure prevents over-generalisation or reliance on clinical or personal experience.

Using this framework to assess the impact on an individual of diagnosis with KS through a screening program identifies key knowledge gaps and areas of incomplete information. Further research is required. In the interim, the implementation of any genetic screening program for KS should initially be regarded as a pilot program, done primarily for research purposes. It should be closely monitored and evaluated, and the data collected from it be used to re-evaluate the appropriateness of the

screening program, before it is extended any further. KS is a pertinent example of a genetic condition where a pilot screening program may be the only way to garner invaluable information about the hidden undiagnosed population, about which we can only currently speculate. These same considerations would apply to other genetic conditions with variable phenotype, strong psychosocial component and interventions of uncertain benefit.

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