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4-1-2017

### Genomic Contraindications for Heart Transplantation.

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#### Recommended Citation

Char DS, Lázaro-Muñoz G, Barnes A, Magnus D, Deem MJ, Lantos JD. Genomic Contraindications for Heart Transplantation. *Pediatrics*. 2017;139(4):e20163471. doi:10.1542/peds.2016-3471

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# Genomic Contraindications for Heart Transplantation

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Genome sequencing raises new ethical challenges. Decoding the genome produces new forms of diagnostic and prognostic information; however, the information is often difficult to interpret. The connection between most genetic variants and their phenotypic manifestations is not understood. This scenario is particularly true for disorders that are not associated with an autosomal genetic variant. The analytic uncertainty is compounded by moral uncertainty about how, exactly, the results of genomic testing should influence clinical decisions. In this Ethics Rounds, we present a case in which genomic findings seemed to play a role in deciding whether a patient was to be listed as a transplant candidate. We then asked experts in bioethics and cardiology to discuss the implications of such decisions.

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## THE CASE

A 12-year-old boy with Tetralogy of Fallot and pulmonary atresia with multiple aortopulmonary collaterals is admitted with worsening heart

failure and is being considered for heart or combined heart and lung transplantation. During extracorporeal membrane oxygenation (ECMO) after a previous heart surgery, the patient experienced a thrombotic event resulting in a left middle cerebral artery stroke, leaving him with right-sided hemiparesis and dysarthria. He has had several venous thromboses, despite normal results on all routine laboratory tests of clotting function. The patient also has developmental delay and hypothyroidism.

Whole genome sequencing (WGS) is performed both to potentially provide a unifying diagnosis for the cardiac defects, hypothyroidism, and developmental delay, as well as (given the complexity of performing heart transplantation in a child who has had multiple prior cardiac surgeries) to screen for genetic variants that might explain the patient's recurrent thrombotic events. Analysis of WGS confirms that the patient has DiGeorge syndrome (DGS), a 22q11 deletion, but also reveals that he has a particular variant of 22qDS highly

## abstract



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All authors contributed to the design of the paper, the drafting of the manuscript, and review of the manuscript; and all authors approved the final version as submitted.

**DOI:** 10.1542/peds.2016-3471

Accepted for publication Oct 20, 2016

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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**FINANCIAL DISCLOSURE:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** Research for this article was supported by National Institutes of Health (NIH) grant K99HG008689 (Lázaro-Muñoz, PI), NIH grant K01HG008498 (Char), and NIH grant U19HD077693 (Lantos). Funded by the National Institutes of Health (NIH).

**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

**To cite:** Char DS, Lázaro-Muñoz G, Barnes A, et al. Genomic Contraindications for Heart Transplantation. *Pediatrics*. 2017;139(4):e20163471

associated with schizophrenia and multiple variants in several other genes associated with schizophrenia, including in his type 2 dopaminergic receptors; these variants make it very likely that he will develop schizophrenia and that the disease may be severe. The patient was adopted, and thus a confirmatory family history is not available.

Given the psychosocial challenges associated with management of a transplanted organ in adolescents, the challenges to self-care posed by the patient's already-present developmental delay and stroke, the scarcity of available pediatric donor organs, and with the WGS findings, the heart failure team decides that they will not go forward with listing the patient for a transplant. Without the prospect of a future transplant, the team feels the patient would be a poor candidate for a ventricular assist device.

The family objects to the team's decision and states that had they known the WGS results could lead to taking away options, they would never have given permission for the test. How should the team respond? Should they have disclosed the possibility that the findings would be used as a basis to deny treatment before testing?"

### **Drs Char and Magnus Comment**

WGS in pediatrics has the potential to create psychosocial burdens on children and their families.<sup>1</sup> This clinical case highlights one of the most severe potential harms: a child may be denied a life-saving therapeutic option (in this case, a transplant organ) based on the results of WGS. This concern is a real possibility. Scarce resources in pediatric acute care (eg, transplantation, extracorporeal oxygenation, complex surgical interventions) are already rationed by clinicians based on the results of the genetic testing currently in clinical use.<sup>2-5</sup> WGS has the

potential to expand the number of genetic findings that may be used as justification for rationing scarce resources.<sup>6,7</sup> This potential use of WGS results is not appropriate. The technology is new and still hard to interpret, the spectrum of false results is still unclear, most WGS findings have not been rigorously studied, and the prognoses stemming from these WGS findings are not well validated.

For genetic diagnoses that already have rigorously studied prognoses, WGS findings (particularly if corroborated with other, established tests) may be used to make a prognosis in an individual child and, consequently, potentially limit access to a scarce resource. The pressure to best triage scarce resources is strong. Acute care resources, particularly transplant programs, need to steward their precious resources toward the children these resources will most benefit. Data that provide guidance for these difficult triage choices are invaluable to these acute care clinicians.

However, the track record for efforts at such stewardship is mixed. Despite growing evidence that developmentally delayed patients have survival rates equivalent to other patients who receive transplants,<sup>8,9</sup> transplant programs often (although inconsistently) use this delay as a basis for denying transplantation. Forty-four percent of US pediatric heart, liver, and kidney transplantation programs report that they "usually" or "always" consider the developmental delay in their decision process.<sup>5</sup> In addition, lung and heart transplantation physicians have explicitly stated that they would also withhold transplantation in children with genetic defects.<sup>4</sup>

Currently, clinicians ration other scarce resources in children based on genetic findings associated with developmental delay, cognitive impairment, and the potential for a poorer prognosis. For example, 91%

of ECMO center directors stated they would not offer ECMO to a child with trisomy 13, and 90% would never offer ECMO to a child with trisomy 18; 32% would not offer ECMO to a child with trisomy 21 who otherwise met criteria.<sup>2</sup> For high-risk surgeries, such as with the complex congenital cardiac disease hypoplastic left heart syndrome, clinicians refuse to operate on some children with trisomies.<sup>3</sup>

As WGS becomes better studied, validated, and implemented, it will allow individualized drug therapies and guide early interventions. However, the results of WGS testing may also be used as justification for declaring futility of care and for guiding scarce resources to another child.

In the present case, the secondary WGS findings became part of the deliberations by the heart failure team in choosing whether to list the patient for potential transplantation. This action is not surprising. As stewards of scarce resources, pediatric transplant programs steer resources to those who will best benefit from them. Such programs also have concerns about graft survival and how poor posttransplant outcomes might reflect on, and impact the survival of, the program itself.<sup>4</sup>

However, there are problems in using WGS findings in this way.<sup>8</sup> The suggestion of the potential for a particular disease or syndrome based on WGS results may not be reliable enough to play such a critical role in life-and-death decisions. This concept is especially true for predictive tests (ie, those which are not used to diagnose disease in a setting of current clinical manifestations but, instead, to predict future onset of disease). Technical concerns regarding understanding all of the potential WGS testing pipeline errors are still being worked out.<sup>8</sup>

Even if the WGS findings were wholly accurate and the subsequent manifestation of disease stemming from the findings is likely, concerns would remain. What sort of future diseases ought to preclude life-prolonging treatment today? It is not obvious that an increased risk of later-onset schizophrenia should be a contraindication to transplant.

Because WGS findings may be used to limit care, it is reasonable to require (at the present time) that all such testing should necessitate a full and explicit informed consent that includes discussion of the ways in which such tests have the potential to be used as part of the triage process and may inform what clinical options are available. Private WGS testing of children (eg, through direct-to-consumer platforms) should be similarly explicit about the longer term implications of the WGS results.

WGS results need to be rigorously studied. Given the complexity of these results, it is unlikely that the bedside clinicians making acute decisions, such as the team in this case example, will be aware of how to interpret all the limitations of particular WGS findings. Additional education and knowledge support will be needed. In addition, as WGS prognostic data emerge, clinicians will need to explicitly and transparently justify their triage decisions surrounding scarce resources to make sure they are cognizant of when they are serving as good stewards of these scarce resources and to protect them from acting in a prejudicial manner toward those with cognitive or behavioral disabilities. Most importantly, for at least the present, clinicians will need to convey the potential for limitations on what care will be offered based on WGS findings as part of the informed consent process to families considering WGS.

### Dr Lázaro-Muñoz Comments

The American College of Medical Genetics and Genomics recommends that before ordering diagnostic WGS for children, the child's parents or guardian should be informed of the potential risks and benefits and asked to provide consent.<sup>10</sup> As fiduciaries, clinicians have a duty to disclose information that is material to making an informed decision regarding WGS and other types of medical interventions.<sup>11</sup> The fact that the WGS results could be used to deny access to a potentially life-saving heart transplant can safely be regarded as material information. This foreseeable consequence of WGS should have been disclosed by the team before the testing was conducted. The family's assertion that they would have never given permission to the test had they known the results could lead to taking away options—although stated in hindsight—further supports the notion that this information is material for informed consent.

One argument against this scenario could be that the test results were not anticipated. They should have been, however. Given the child's clinical presentation (ie, congenital heart disease, developmental delay, hypothyroidism), it was anticipatable that WGS could reveal 22qDS, a variant that is known to be associated with schizophrenia.<sup>12</sup> Therefore, the potential for an incidental finding of increased risk for schizophrenia, which would have implications for the child's psychosocial evaluation as a transplant candidate, was foreseeable. Because it was material for decision-making, it should have been communicated during the consent process. At a bare minimum, guidelines suggest that the team should have disclosed the possibility of incidental and secondary target findings with WGS that might have led to reconsideration of the child's eligibility for transplant.<sup>13,14</sup>

Failure to disclose all this information restricted the family's ability to decide what was in the best interest of their child regarding WGS. The surprise of learning that the WGS results would be used to deny medical options likely made the family feel misinformed, and perhaps deceived, by the clinical team. This situation can negatively impact the trust necessary for an effective clinician-patient relationship.<sup>15</sup>

Disclosure oversights are likely to occur when introducing novel technologies in medical care. However, there is a growing body of literature that addresses how to anticipate and manage many of the issues regarding incidental findings of WGS.<sup>16-18</sup> As WGS becomes more accessible and common in clinical practice, clinicians must not only stay abreast of data about the clinical usefulness, technological capacities, and limitations of WGS, but they must also be prepared to address the clinical ethics challenges and potential harms that genomic testing can generate.

Presumably, the WGS results suggesting an increased risk for schizophrenia played an important role in the team's decision not to list the child for a transplant. The other psychosocial challenges (eg, difficulties of self-care because of developmental delay and stroke, patient near adolescence) were already present before WGS. However, these results should be interpreted with caution. The genetics of schizophrenia are becoming clearer,<sup>19-21</sup> but many ambiguities and uncertainties remain. For example, although earlier reports estimated the penetrance of schizophrenia in 22qDS to be as high as 55%,<sup>22</sup> recent studies with larger samples suggest it is as low as 12%.<sup>23</sup> Thus, the clinical team should reconsider the weight it gave to the schizophrenia-associated variants and consult with a medical geneticist or genetic counselor before making



a final decision about the child's candidacy for transplantation.

Moving forward, the team should call for an ethics consult or identify a team member that has rapport with the family to help facilitate communication. The team should have a frank discussion with the family to explain the difficult patient-centered and public health interests that must be balanced when determining whether to list a child as a transplant candidate and why they felt they could not list this child. As part of that discussion, the team should clarify why they did not disclose that WGS results could be used to deny access to certain medical options and ideally apologize for this omission. In addition, the team should advise the family about alternatives, including the possibility of other programs that may accept the child as a transplant candidate. Above all, they should remain available to assist the parents in their ongoing decisions about their child's health care.

### Dr Barnes Comments

Families hope and expect that data will point to a clearly optimal choice regarding the best decision for their child. Physicians and families both hope for a choice that will lead to the child being well again. They want to be able to look back on the nightmare of life-threatening illness as a distant memory.

Cardiac transplantation is typically a last option. Usually, if a transplant is not possible, the child will die. Families think of transplant as the one choice that will fulfill their hopes for cure.

A transplant physician and team are charged with many critical responsibilities. There are misconceptions that must be clarified, expectations that must be realistic, and concepts that must be understood before physicians, patients, and families start the

transplant journey together. Effective communication is critical. Some of the key concepts in this communication process include:

1. Transplant involves trading one set of issues for a different set of issues. Transplant is not a cure. A transplant parent never stops worrying what the next day will bring due to the major complications of rejection, infection, and cancer. These issues can occur on day 1 of transplant or 20 years later. A transplant patient will be taking time-sensitive medications for life. Patients will have physician appointments, laboratory tests, and studies for the rest of their life. It is imperative that the family fully understands the importance and complexity of adherence in the life of a transplant patient.
2. There must be a very thorough evaluation before listing a patient for transplant. We must help families understand that the evaluation is to be sure that the procedure transplant and life after transplant are going to be successful. We must help families to understand that the purpose of the pretransplant evaluation is to maximize the chance that the procedure will be successful. They should understand that, as part of this evaluation, we will do a number of tests that may change our recommendations about whether to recommend a transplant. At times, there are unique issues that cannot be predicted but still serve as a contraindication to transplant due to their likely negative impact on transplant outcomes.
3. The decision of whether a patient will be listed is mandated by the government to be a decision made by a multidisciplinary group of experts based on their opinion of the likelihood of positive outcomes. This conclusion is a grave decision that must be

critically discussed and cannot be based on 1 person's thoughts or analysis. A group of experts that represents all aspects of the patient's care discuss all findings of the evaluation and decide if any additional testing should be conducted or if there is adequate information to make a decision. Any additional testing is to be sure that any important information is not missing that may make the transplant a failure.

4. Being placed on the transplant waiting list does not guarantee that a child will get a heart transplant. Families must understand ahead of time that listing for cardiac transplantation is a dynamic situation. Even if a patient is listed, the patient will be evaluated regularly to determine if he or she is still a candidate who will likely have a successful outcome. If there is any change or additional information is revealed, it may or may not affect listing status, and the family should be fully informed of this possibility. This juncture is where we explain the use of Status 7. Status 7 on the transplant waiting list indicates that the patient is still on the list but will not receive new organ offers. The transplant team will use this status until any new questions are fully investigated and will not accept a heart until they again know it will be a success. Families also need to understand that children may get too sick before a heart becomes available because it is such a scarce resource. Death while on the waiting list is always a possibility, and families must be prepared for this possibility.

All of these important aspects and more must be discussed with the family before starting the heart transplant evaluation. Most centers have a "transplant talk" that can take anywhere from 45 minutes to 3 hours. Most centers feel this

talk is so important that there is a signed consent to evaluation that the parents must agree to before starting the evaluation.

The question arises regarding whether transplant teams can ever achieve fully informed consent from families related to transplant. The families are often emotional and traumatized, reeling from the thought that their child needs a transplant. Many times, as in this case, this finding is just one more piece of traumatic bad news in a line of frightening information and experiences for the child and the family. We know that when parents are that emotionally stressed, they do not understand or retain information. But what choice do we have?

It is the transplant team's burden to try to assess parents' understanding, work at ways to help them cope with the stress, and help them understand the information that we are providing. One strategy to address these concerns involves having the psychosocial team assess how the family learns best. In addition, psychologists can evaluate the level of emotional stress and capacity, and other team members may check understanding and fill in any gaps that are found with repeated conversations. The family is given the written consent to read later for better comprehension. Most centers have a transplant book for parents that includes abundant information about transplant life and the evaluation.

Although we try, it is impossible to explain everything that may be uncovered on a pretransplant evaluation. Perhaps, in the present case, the team did try to explain at least the possibility of something being found that would change their thoughts regarding the patient being a good candidate for transplantation. Perhaps the family did not hear or understand that information in their emotional state.

In this situation, I believe that the team should stress that the decision to not list for transplantation was not based solely on the WGS test result but the combination of issues that made the patient a high-risk candidate. The family needs to understand that the physicians are not taking away an effective treatment but are, instead, trying to avoid the likelihood of an unsuccessful transplant. To reinforce this approach, they should offer to send the patient's data to another center for a second opinion if the family desires. In this case, I believe a majority of centers would agree with the final decision due to the many serious medical issues.

The bottom line is that transparent and clear communication are crucial from the beginning but are sometimes thwarted by the stressful and emotional state the family and team function in every day. It is impossible to prepare families for everything, but being sure to cover the critical concepts in a way families can comprehend usually paves the way to well-prepared families and open lines of communication for hard conversations.

### **Dr Deem Comments**

This case highlights an important ethical question associated with the clinical application of WGS. Given WGS's potential to affect clinical management in ways a patient or his or her surrogates might regard as harmful, do clinicians have a duty to disclose that possibility during the consent process for WGS?

On the basis of the medical team's stated aim in ordering WGS, as well as the parents' reaction to the team's decisions, we may reasonably infer that the parents did not possess adequate information about the potential impact of WGS on their child's clinical management. When patients or their surrogates hold inadequate information about the possible benefits and risks

of a proposed medical test or treatment, their ability to make informed medical decisions is compromised. It is reasonable for patients or their surrogates to view denial of treatment as a foreseeable, unwanted, and harmful effect of WGS. This risk ought to be disclosed and clarified when patients or their surrogates consider WGS. The team, then, had a duty to disclose the possibility that WGS findings would be the basis for the denial of certain treatments. If that information was not provided to the parents, the consent process for WGS was ethically problematic, and their opposition to the decision is warranted.

The ethical problems in this case do not stem solely from the consent process. Although the team's reluctance to list the patient for transplantation is understandable, there are grounds for questioning the strength of the reasons the team offered to justify its decision. Let us briefly consider each reason the team offered.

### *Psychosocial Challenges*

Tetralogy of Fallot typically requires multiple surgeries beginning in infancy. Given the co-presentation of pulmonary atresia and aortopulmonary collateral arteries in this case, we may conclude that the patient required staged repairs.<sup>24</sup> Moreover, 22q11.2 deletion syndrome is associated with longer postoperative intensive care.<sup>25</sup> Having already faced the psychosocial challenges of several complex pediatric surgeries and postoperative care, this particular family is likely well acquainted with, and well prepared to handle, the challenges arising from pediatric transplantation.

### *Challenges to Self-care*

How the patient would manage the challenges of self-care after transplantation depends on a number

of factors. The child currently exhibits developmental delay, but it is difficult to predict how his cognitive disability and thrombotic history will affect him as an adult. The degree of cognitive disability in persons with DGS is highly variable. We do not know whether the patient will be responsible at some point for his own care or instead will receive continuous care from family or specialists. Without consulting the parents, the team is not in a good position to predict the long-term challenges to the patient's care.

### Scarcity of Donor Organs

Scarcity of pediatric donor organs is not itself a reason to deny listing for transplantation in a particular case. Rather, scarcity is a background condition of all transplantation cases against which hospitals and medical organizations ought to develop allocation mechanisms that are just. If there is good evidence that the transplantation would be futile or lead to a poor outcome, then these would be ethically defensible reasons for withholding transplantation. In this case, the team did not offer such evidence to support its decision.

### The WGS Findings

Of the 4 reasons provided as justification for the team's decision, the WGS findings seem to be doing the most work. The first 3 reasons were presumably weighed when the patient was initially considered for heart transplantation (before WGS), and the team reached the decision not to move forward with listing only after the WGS findings were returned. Why did the genetic diagnosis lead to this decision?

A diagnosis of DGS does not itself indicate that heart transplantation would result in a poor outcome. The phenotypic presentation of DGS is extremely variable, and there is a great deal of clinical uncertainty with respect to posttransplantation outcome. Moreover, the team

would have been familiar with the patient's phenotypic presentation when he was initially considered for transplantation, and the patient was not determined to be a poor candidate for transplantation at that time. The WGS findings show that the child's cognitive disability is likely to become more severe as he matures and that there is a high probability that he will develop adult-onset psychiatric illness. But these possibilities would not provide justification for a unilateral decision to deny transplantation. It is unclear, then, why the genomic results so strongly affected the team's deliberation.

If, as seems to be the case, the consent process did not include disclosure of the potential impact of WGS on the patient's management, then the parents' objections are justifiable and appropriate. The team ought to seek to revisit treatment options with the parents. The parents should be involved in the decision-making about listing for transplantation and/or using a ventricular assist device. Initiating this conversation might go some way toward reestablishing trust between the parents and the team. It also would be an opportunity for the team to gather more information about the parents' already extensive experience handling the challenges of postoperative care for their child, their ability to provide adequate posttransplantation care, and their perception of their own abilities to provide that care. Without discussing these matters with the parents, the team is in no place to determine how prepared the family is for the psychosocial challenges and complex care the patient may require. Reopening this discussion need not require that the team abandon its original concerns about listing for transplantation. But these concerns should be expressed at the beginning of the conversation with the parents about treatment options.

### Dr Lantos Comments

This case brings together 3 of the most controversial issues in pediatric bioethics today: the allocation of organs for transplantation, the use of genome sequencing to predict future health problems, and the assessment of quality of life. It is not surprising to find disagreement among experts. The allocation of scarce resources requires robust theories of justice and political integrity in applying those theories to the real world of individual patients and families who might benefit or be harmed unjustly. Genomics requires humility in the face of highly uncertain and probabilistic findings that we know, given our current state of understanding, can only be tentative and are likely to be inaccurate. The only way to muddle through this domain of uncertainties will be by carefully and humbly presenting and analyzing cases like this one to determine when and whether genomic findings should be part of the equation of organ allocation. We welcome reader comments on this case and presentation of other cases that raise similar issues.

#### ABBREVIATIONS

DGS: DiGeorge syndrome  
ECMO: extracorporeal membrane oxygenation  
WGS: whole genome sequencing

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*Pediatrics* 2017;139;

DOI: 10.1542/peds.2016-3471 originally published online March 2, 2017;

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Danton S. Char, Gabriel Lázaro-Muñoz, Aliessa Barnes, David Magnus, Michael J. Deem and John D. Lantos

*Pediatrics* 2017;139;

DOI: 10.1542/peds.2016-3471 originally published online March 2, 2017;

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