Received: 9 February 2022 | Revised: 19 May 2022 | Accepted: 4 July 2022

DOI: 10.1111/ctr.14769

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

ORIGINAL ARTICLE

Organ donation from patients with a rare disease is often safe: the italian guidelines

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Abstract

Although a disease is defined as rare when it has a prevalence of less than 1:2000, the overall prevalence of rare diseases in the population is greater than 1%. Among potential organ donors, a similar frequency is observed. To date, guidelines have not been established, and operational decisions have been made empirically, case- by-case, based on the experience and expertise of clinicians. For this reason, the Italian Superior Health Council (CSS) has appointed a working Group to address "patients with a rare disease as potential organ donors," with the aim of devising recommendations for the management of transplant cases in which the donors have a rare disease. This group evaluated 493 diseases (10% of all rare diseases, including over 95% of patients with a rare disease) to deliver a technical report dealing with the suitability of organ donation and transplantation, with a focus on the organs most frequently used, including kidney, liver, heart, lung, and pancreas. This work has made it clear that a rare disease "per se" does not contraindicate organ donation at all. Indeed, in donors affected by a rare disease, almost 80% of the organs are suitable for transplantation, approximately 7% are

unsuitable, and approximately 14% are suitable as non-standard with an acceptable risk.

KEYWORDS
guidelines, organ donors, rare disease, risk assessment

1 | INTRODUCTION

The European Union Committee of Experts on Rare Diseases defines rare diseases as those occurring at a frequency of less than five cases per 10 000 people. Overall, rare diseases affect at least one million patients in Italy (excluding rare cancers) and approximately 30 million people in Europe.

The list of rare diseases includes more than 7000 conditions, a number that is variable in relation to the classification method. Among these rare diseases, 84% are ultra-rare, affecting less than one person per million citizens. Approximately 150 diseases account for 80% of all rare disease cases, 50%–60% of which have their onset during the pediatric age, and about 80% have a genetic origin. It is estimated that 6% of patients with rare diseases remain undiagnosed, but this figure could be as high as 50% in children with mental disability and complex phenotypes.

In consideration of their overall frequency, a diagnosis of rare disease is expected to be present in a considerable number of potential organ donors, raising the question of whether it can contraindicate transplantation.

Although "zero risk" organ transplants do not exist because the procurement process takes place under emergency conditions, the evaluation process of the donor organ and tissue is aimed at minimizing the risk of transmitting a disease to the transplant recipient. The assessment of the individual organ candidates for transplantation must guarantee the recipient a real benefit from the transplant. Based on the clinical diagnosis, medical history, physical examination, blood chemistry, and instrumental evaluations of the donor, different situations may emerge. In this scenario, it is always and, ultimately, the responsibility of the clinician who manages the recipient awaiting transplantation to assess the most acceptable risk, referring to a given patient, between staying on the list for an indefinite period, or receiving an organ potentially capable of transmitting a particular disease or one that is considered non-optimal.[1]

The dividing line between determining that an indispensable and rare gift is unsuitable and ensuring that a transplant is performed with relative safety and a feasible organ is not always clear. Therefore, a careful evaluation of the affected organs (as in the case of multisystem disorders), the function of a potentially transplantable organ (in the case of some inherited metabolic diseases, it is possible that an alternative pathway overcomes the defect), and the possible risk of developing neoplasms related to the underlying disease is necessary. In the latter case, previous immunosuppressive therapies could also act as a catalyst for the onset of cancers in the transplanted organ.

Organ transplantation from donors with rare diseases is limited. To date, guidelines have not been established and, in general, operational decisions have been made empirically, case-by-case, based on the experience and expertise of the involved clinicians.

1.1 | Rare diseases

In recent years, rare diseases have received focused attention. Historically, a disease's rarity was associated with its diagnostic complexity, making it difficult to develop effective treatments. The adoption of the prevalence threshold enabled identification of rare diseases in legislation, thereby promoting the research and development of orphan drugs in the United States[2] and then in Europe. Yet the prevalence rates of rare diseases are highly variable in different countries, ranging from less than 1:20 000 in South Korea to less than 1:1350 in China and 1:2000 in Europe.[3] Despite the lack of a universally accepted definition,[4] rare diseases are considered a priority in both research initiatives and public health.[5] The rarity of individual conditions in many cases results in diagnostic delay, as distinct clinical handles are often lacking. Although the situation has improved in recent years, diagnostic delays remain an issue and, even worse, a high proportion of patients remain undiagnosed. Finally, the patients' management is challenging; only about 5% of rare diseases have effective therapies, which result in reduced life expectancies in about two-thirds of the cases.[6]

Rare diseases, therefore, represent a complex medical problem that demands specific competence and specialization, both for their diagnosis and management, which require continuity and a multidisciplinary approach. In fact, one common aspect of their complexity is the simultaneous or successive involvement of several organs. The Orphanet database reports that only 5% of rare diseases affect a single system or organ; about two-thirds affect two or three systems or organs, and about one-third affect four or more systems or organs.[7]

The natural history and mechanisms underlying interindividual clinical variability of many rare diseases is not well understood, although next-generation sequencing tools are expected to improve the ability to better depict genotype-phenotype correlations.[8]

Approximately 6%–8% of the European population is often reported as being affected by a rare disease, although this estimate is not based on a population study. An Italian report, referring to a population register and 10-year monitoring, suggested that rare diseases affect between 1.3% and 2% of the population, excluding and including rare tumors, respectively.[9]

A study of 323 rare diseases revealed that 25.7% of patients died before the age of 5 years; 36.8% had a reduced life expectancy, and in 30%, the rare disease had no impact on life expectancy.[10] Another study assessed the natural history of 430 Mendelian diseases and confirmed that in about one in three the life expectancy was not changed,[11] while it was mildly reduced in 16% of diseases, moderately reduced in 20%, and significantly reduced in 29%. The same study pointed to disease onset in the pre-reproductive age in 85% of diseases, and multisystem involvement in 70% of diseases.

Another critical point that needs to be focused are transplants, which deserve a critical evaluation not only as potential lifesavers in affected patients with rare diseases, but also as potential gifts from patients with rare diseases to the benefit of other diseased individuals needing organ transplants, an issue that applies to 1%–2% of organ donors.

1.2 | Clinical risk management in transplants

In 2002, the Italian Transplant Network drafted the first edition of the "Protocol for the assessment of suitability of the donor of solid organs" with the purpose of supporting operators and harmonizing the evaluation of donors. The donation process is complex and often burdened by the need to respect very tight deadlines and by the impossibility of carrying out diagnostic investigations requiring an extension of the donor's maintenance times or his/her transfer to other departments. This protocol was updated and the latest version, approved by the National State-Regions Conference (CSR 17/2018),[1] provided for the preparation of technical annexes concerning hematological and oncological disorders and infectious diseases, with the aim of minimizing the risk of disease transmission from donors to transplant recipients.

Major transplant-related communicable diseases include infectious and neoplastic diseases. Alongside these macro-categories, other conditions must be considered, which, although not directly transmissible, can result in organ damage or predispose to organ damage, jeopardizing its functional quality.

Therefore, the assessment process for donor suitability must be considered as a process aimed at collecting, through anamnesis, laboratory investigations, clinical examination, observation in the operating room, and histological assessments when necessary, as much information as possible, to ascertain the existence of diseases that could be transmitted from the donor to the recipient. For communicable diseases, this means those for which available scientific evidence supports a risk of transmission, not as "possible," or "presumable," but as "actual."

However, not all situations in clinical practice can be framed within the provisions of the national guidelines. For this reason, in 2004, the National Transplant Center (CNT) requested some experts (infectious diseases, pathologist, hematologist, and immunologist) to be entrusted with the task of suggesting, based on their professional experience and scientific literature, the most appropriate method of managing the situation represented (wherein a second opinion provides for the definition of the judgment of suitability and the corresponding risk profile).

Thus, assessment of the suitability of the organ donor is a multiphase and multidisciplinary process that involves all operational levels of the transplant network (from hospital and regional coordination to national transplant coordination). The definition of the suitability judgment and the corresponding risk profile is finally defined by regional coordination, in agreement with the national transplant coordination.

Based on data collected, potential donors are classified as suitable or unsuitable. Different levels of risk were identified among suitable donors, as shown in Table 1.

For non-standard donors, recipients should give specific consent at waiting list enrolment, as well as at the time of transplantation. A donor is considered unsuitable if there is a risk of disease transmission, the severity of which exceeds the expected benefit from the transplant or the risk of mortality resulting from the recipient's stay on the list.

1.3 | Definition of the suitability and risk profile of the organ donor affected by a rare disease

Potential donors affected by rare diseases are uncommon, excluding hematological and neoplastic diseases. Nevertheless, between 2017 and 2019, the CNT reported that approximately 1% of Italian potential donors had a rare disease.[12]

The transmission of these diseases from the donor to the recipient has not been reported; however, a careful and rapid evaluation of the target organ(s) of the disease is mandatory, considering that many rare diseases are multisystemic, some confer susceptibility to cancer development, and post-transplant immunosuppressive therapy could act as a catalyst for the onset of neoplasms. In addition, in the case of inborn errors of metabolism, it is possible that alternative pathways may overcome the constitutional defect.

When the diagnosis of a rare disease is not definitively ascertained, extensive clinical screening is required that can eventually involve other family members and may require extensive genetic testing, which takes time and, in general, is not compatible with the urgency of the donation and transplant processes. Often, the functionality and level of organ damage must be assessed individually by means of histological investigations.

The diagnosis of several rare diseases and latent metabolic defects (e.g., ornithine transcarbamylase deficiency) is difficult because, at the time of donation, not all the clinical symptoms may be present, but they can manifest in the recipient. Other multisystem diseases, despite sparing organs, affect tissues that jeopardize the surgical act of transplantation (i.e., defects in the elastic tissue undermine the surgical repair of vessels).

The emergency section of the Orphanet database quotes transplantation in several diseases, but the list is not exhaustive. The "Guide to the quality and safety of organs for transplantation. EDQM

TABLE 1 Donor eligibility

Suitable donor at standard risk	Suitable donor at non-standard risk		
	with negligible risk profile	with acceptable risk profile	with acceptable risk profile for patients in serious clinical condition
Absence of risk factors for disease transmission from donor to recipient	Presence of risk factors for disease transmission with no different probability of organ or patient survival compared to recipients' organs from donor at standard risk; no restrictions in the selection of recipients.	Presence of risk factors for disease transmission with no different probability of organ or patient survival compared to recipients' organs from donor at standard risk; no restrictions in the selection of recipients.	Presence of risk factors for the transmission of diseases, such as to entail specific restrictions or recommendations for the recipient. The risk is considered lower than the risk resulting from the recipient remaining on the waiting list. Presence of risk factors for the transmission of diseases, such as to involve the use of organs only for patients for whom it is possible to foresee a potential benefit despite the greater risk of transmission of disease (recipients in imminent danger of life).

7th edition 2018 by the Council of Europe"[13] provides an additional source of information on the possibility of using individuals with rare diseases as donors, but again the list of disorders is not comprehensive of those found in clinical practice.

In the presence of a rare disease, the risk level should not be attributed to the donor as a whole, as in the case of infectious and neoplastic diseases, but to the individual organs. An illustrative example is offered by some inborn errors of metabolism-affecting pathways present exclusively in the liver, such as urea cycle enzymes. The transplant of organs not involved in this metabolic pathway, notably the heart and kidneys, is considered safe.

In the case of several potential donors affected by rare diseases, the CNT's experience has shown the possibility of profiling the risk of individual organs, both in terms of disease transmission and functional suitability, to guarantee that the recipient will benefit from the transplant.

1.4 | How to classify rare diseases in the context of organ donation

Rare diseases are highly heterogeneous, and their clinical characteristics can hamper the use of affected individuals as potential organ donors. Some diseases can even put the recipient's life at risk. The use of organs from donors with rare diseases must undergo preliminary checks for the following:

- The possibility of disease transmission in the recipient (i.e., some diseases are caused by a defect in an enzyme produced by the liver; following the liver transplant, the recipient would be unable to produce the relevant enzyme and develop the disease).
- The presence of underlying diseases, based on which the donated organ could lose its function, putting the recipient's life at risk (i.e., heart failure or rhythm disturbances, after heart transplantation).

In the case of a suitable donor affected by a rare disease, each organ should be assigned a risk level based on several queries, including cause of death, age of the donor, identification of the metabolic deficit, target organs and secondary organs involved, phenotypic variability, connective tissue diseases, neoplastic risk, clinical condition of the donor, and effectiveness of domino transplantation.

1) Cause of death

Cardiac or brain death can have different etiologies. In the case of a potential donor affected by a rare condition, it must be confirmed that any multisystem widespread damage caused by the disease's progression has not affected the target organs. Therefore, these donors need thorough evaluation. Ammonia measurements are recommended for all donors with an unclear diagnosis of brain death, which is associated with disorders of the urea cycle.

2) Age of the donor

The age of the donors is important for risk assessment. In the case of a pediatric donor, the absence of organ damage does not exclude the possibility that damage may occur in the recipient after some time. Organ damage caused by rare diseases can take a long time to become clinically appreciable. Therefore, it is possible that organ damage has not yet manifested in young donors. In the case of an adult donor, if organ damage is not present at the time of donation, the risk level can be considered low. Some rare diseases become symptomatic early in life, while in older ages, they display less severe symptoms, suggesting that the donor has a relatively mild disorder and likely less important organ damage.

3) Identification of the metabolic deficit

In some cases, the metabolic deficit affects a distinct enzyme pathway, which is operational in a single organ, mostly the liver. In the absence of alternative pathways, the defect is transmitted with the transplant of the relevant organ, with no possibility of recovery by other organs. The defect can account for variable clinical features, some of which are solved by replacement therapy, while others are incompatible with life. Therefore, the target organs cannot be used for transplantation.

4) Target organs and secondary organs involved

It is necessary to distinguish whether the organ damage associated with a given disease is primary or secondary to a defect in a different target organ. It is expected that the potential damage in the untargeted organ transplanted into an unaffected recipient will not progress or regress.

5) Phenotypic variability

Many Mendelian disorders manifest interindividual clinical variability, even in the presence of the same pathogenic mutation. Thus, the extent of organ damage after transplantation cannot be accurately assessed. Environmental factors and modifying genes can be drivers of unpredictable injury in transplanted organs.

6) Connective tissue diseases

Although the function of organs at the cellular level may be normal, the transplant could be complicated by the difficulty in sewing blood vessels due to structural damage to the wall (e.g., Marfan syndrome). The final decision on the use of these organs is the responsibility of the surgeon in charge of the transplant.

7) Neoplastic risk

Some rare diseases present a high hereditary risk of developing cancers, which are often located in multiple organ systems. Thus, at the time of organ donation, the presence of neoplasms should be carefully monitored. In the absence of tumors, the risk of cancer must be monitored in the recipients, and immunosuppressive therapy should be modulated to decrease the neoplastic risk.

8) Clinical condition of the donor

An accurate clinical assessment of the donor before death is mandatory, mainly for an appraisal of the severity of the underlying rare disease. Important clinical symptoms, congruent with those of the rare disease, may be suggestive of a greater severity of the disease.

9) Effectiveness of domino transplantation

Sporadic reports have illustrated the use of organs in the so-called "domino" mode.[14] These include mostly liver transplants and sometimes kidneys from living donors affected by a disease, usually rare and genetic in nature, who received a transplant, while their native organ was used for transplantation in another recipient. The rationale for this procedure lies in the fact that if the replaced organ has suffered secondary damage due to a disease, it can be effectively used in a recipient not affected by the same disease. The information derived from these cases is useful for understanding whether organs from donors with rare diseases can be safely transplanted.

All these queries are summarized in Table 2.

TABLE 2 Factors to be considered in assigning a risk level to the organs

Factors	Detail
Cause of death	Ammonia measurements are recommended for all donors with an unclear diagnosis of brain death to exclude urea disorders
Age of the donor	In paediatric donors, organ damage can be non-developed jet, but can be developed years later in the organ recipient. In adult donors, the presence of less severe symptoms suggests a mild disorder and likely less important organ damage
Identification of the metabolic deficit	In case of metabolic disorders of a specific pathway, verify the presence of alternative subways in other organs that can supply the deficit.
Target organs and secondary organs involved	It is necessary to distinguish whether the organ damage associated with a given disease is primary or secondary to a defect in a different target organ
Phenotypic variability	Environmental factors and modifying genes can be drivers of unpredictable injury in transplanted organs
Connective tissue diseases	the transplant could be complicated by the difficulty in sewing blood vessels due to structural damage to the wall
Neoplastic risk	the presence of neoplasms should be carefully monitored and, even in the absence of tumors, the risk of cancer must be monitored in the recipients
Clinical condition of the donor	An accurate clinical assessment of the donor before death is mandatory, mainly for an appraisal of the severity of the underlying rare disease
Effectiveness of domino transplantation	In many cases, if the replaced organ has suffered secondary damage due to a disease, it can be effectively used in a recipient not affected by the same disease

Given that only sporadic scientific evidence is available on the outcome of transplants from donors affected by rare diseases, the CNT is gathering a targeted collection of data to evaluate the results in recipients of organs from rare diseased donors, to obtain evidence for the safe use of their organs.

A definite diagnosis of a rare disease is not always available at the time of brain or heart death. Often, the diagnosis is only suspected based on clinical characteristics, but not corroborated by appropriate genetic or metabolic testing. On the other hand, these analyses can take a long time, which is not compatible with donations. For this purpose, we suggest the following recommendations:

- Collect all available data and consult clinicians who were in charge of the patient. It would be useful for regional transplant coordinators to access already available data pertaining to the donor, including the diagnostic assessment and previous treatments.

TABLE 3 Rare diseases excluded from the evaluation as the national transplant network has second opinion

Rare diseases of interest	Number of diseases	% (*n*: 493)
Oncological	64	13.0
Hematological	30	6.1
Immunological	30	6.1
Infectious disease	28	5.7

- Investigate the morphology and function of each organ or tissue considered for sampling and exclude organs with significant functional impairment or anatomical damage.
- Check the risk that organs taken from donors with rare disease transfer the genetic defect into the recipient and the transplant recipient becomes affected. The risk of transmission must be proportional to the clinical condition and urgency of the recipient.
- Arrange a collegial evaluation using a multidisciplinary approach involving national experts (second opinion).

Currently, rapid genetic tests are available for diagnosing only a negligible number of rare Mendelian diseases. The management time of the donation process lasts approximately a few hours; a period that is generally not adequate to complete a genetic test before transplantation. Nevertheless, whenever a rare monogenic disorder is suspected in a potential organ donor, the acquisition of biological samples for genetic testing is highly advised because the results may be useful in the recipient's follow-up.

2 | MATHERIALS AND METHODS

2.1 | Evaluation of organ donation in rare diseases

In light of these considerations, The Italian Superior Health Council (Consiglio Superiore di Sanità: CSS) has appointed an interdisciplinary working Group to address "patients with rare diseases as potential organ donors," with the aim of devise recommendations for the management of transplant cases in which the donors have a rare disease. The working Group, composed by experts of medical genetics, internal medicine, metabolic disease, physiopathology, endocrinology, neurophysiopathology, and other clinical fields, has analyzed most frequent rare diseases, making a review of available literature, case reports, personal expertise, and professional-specific knowledge during several virtual and in presence meetings.

3 | RESULTS AND CONCLUSIONS

3.1 | Operational instructions in the management of organ donors with a rare disease

The working group evaluated a group of rare diseases[15] to deliver a technical annex dealing with the suitability of organ donation and transplantation, with a focus on the organs most frequently used, including kidney, liver, heart, lung, and pancreas.

All rare diseases with a prevalence of >2/100 000 or with a prevalence >1/100 000 and an increased risk of death from a neurological diagnosis were examined. From the Orphanet database, we selected 493 diseases (10% of all rare diseases, including over 95% of patients with rare diseases), for which the working group has defined the suitability or non-suitability for donation, and, in the case of suitability, which organs could be used for transplant purposes.

Eligibility for donation was initially defined for each disease. Diseases for which the National Transplant Network has an already established the Second Opinion procedure were excluded from this evaluation, as reported in Table 3.

Excluding the diseases listed in Table 3, 342 clinical conditions (69.4% of all examined) were assessed, as summarized in Table 4.

The presence of a rare disease in the potential donor was unlikely to be the cause of exclusion.

For each disease for which donation suitability (standard or non-standard) was identified, the suitability for organ transplantation was assessed (Table 5).

In conclusion, in donors affected by a rare disease (previously not intercepted by the expertise of the second opinion network experts), almost 80% of the organs are suitable for transplantation, approximately 7% are unsuitable, and approximately 14% are suitable as non-standard with an acceptable risk. For the latter category of organs, a specific follow-up is highly recommended, according to the CNT's indications.

Concerning mitochondrial diseases, their wide clinical and genetic heterogeneity makes it difficult to accurately assess their prevalence, which has been estimated to be approximately 1 in 5000.[16] Over 300 nuclear genes and many mutations in mitochondrial DNA have been associated with these diseases.[17] While pediatric patients have a high proportion of recessive forms, in the adult population, in which these diseases are more common, mutations in the mitochondrial DNA are found in 50%–70% of cases.

From a clinical point of view, mitochondrial diseases often manifest as systemic disorders with multiorgan involvement. The most frequently affected organs and systems include the central nervous system, skeletal muscle, myocardium, and eyes. In pediatric patients,

TABLE 4 Suitability of the rare diseases analyzed

Eligibility for donation	Non-standard eligibility	Non-eligibility	Eligibility not defined in the absence of an etiological diagnosis
291 (85.1%)	16 (4.7%)	2 (.6%)	33 (9.6%)

TABLE 5 Suitability in relation to the transplantable organs

	Suitable		Suitable nonstandard		Unsuitable		
Organ	*n.*	%	*N*	%	*n.*	%	Total
Kidney	244	79.5	48	15.6	15	4.9	307
Heart	223	72.2	54	17.5	32	10.4	309
Lung	246	80.1	42	13.7	19	6.2	307
Liver	245	79.8	38	12.4	24	7.8	307
Pancreas	264	85.7	32	10.4	12	3.9	308
All	1222	79.5	214	13.9	102	6.6	1538

the liver, kidney, pancreas, and endocrine system are commonly involved. Several mitochondrial syndromes are known (e.g., MELAS, MERRF, PEO, Leigh, Kearns Sayre, Alpers, MNGIE) to result from distinct genetic variations, with different clinical outcomes and organ involvement.

Due to the high heterogeneity of mitochondrial diseases, the decision on the use of organs from a potentially affected donor requires a precise genetic diagnosis and, in general, classifies all the conditions at nonstandard risk.

The technical Annex provides, for each rare disease considered, an indication of the suitability for donation and details on the transplantable organs and the level of risk (Supporting Information). This operational tool is basically a general guideline directed to the Italian procurement network for the assessment of donors diagnosed with a rare disease. The appraisal of the donor's risk and suitability of organs proposed for transplantation according to the CNT guidelines remains a central step.

AUTHOR CONTRIBUTIONS

Bruno Dallapiccola, Massimo Cardillo, Antonio Amoroso: Participated in project organization and coordination, evaluation and discussion of the risk for the analyzed rare diseases and writing of the paper. Stefano Moriconi: Participated in project organization and coordination. Michele Colledan: Participated in project organization and coordination and the evaluation and discussion of the risk for the analyzed rare diseases. Massimo Rugge, Carlo Carcassi, Luca Dello Strologo, Carlo Dionisi Vici, Paola Facchin, Bruno Gridelli, Valentino La Rocca, Letizia Lombardini, Monica Mazzucato: Participated in the evaluation and discussion of the risk for the analyzed rare diseases. Daniela Peritore: Participated in the evaluation and discussion of the risk for the analyzed rare diseases and writing of the paper.

ACKNOWLEDGMENTS

We thank to the support and cooperation of the Italian National Transplant Network. Our deepest gratitude is for the donor families, whose generosity makes, each day, transplantation accessible for many patients. This study was supported by a grant from the Italian Ministry of Education, University and Research-MIUR "Progetto strategico di Eccellenza Dipartimentale" #D15D18000410001 to the Department of Medical Sciences, University of Turin.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

This is not an article that analyses numerical data, but diseases present in a list (https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf).

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REFERENCES

1. Solid Organ Donor Suitability Assessment Protocol, defined by the Italian law: CONFERENZA STATO-REGIONI DEL 24.01.2018: Accordo, ai sensi dell'articolo 4 del decreto legislativo 28 agosto 1997, n. 281, tra il Governo, le Regioni e le Province autonome di Trento e Bolzano sul documento recante "Protocollo per la valutazione di idoneità del donatore di organi solidi". Repertorio Atti n: 17/CSR del 24/01/2018
2. United States Food and Drug Administration. *Orphan Drug Act*. Public Law No. 97–414 96 Stat. 2049. 1983.
3. European Parliament and the Council of the European Union. Decision No 1295/1999/EC of the European Parliament and of the Council of 29 April 1999 adopting a programme of Community action on rare diseases within the framework for action in the field of public health (1999 to 2003). 1999. Accessed August 26, 2021. http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1395750802170&uri=CELEX:31999D1295
4. Richter T, Nestler-Parr S, Babela R, Khan ZM, Tesoro T, Molsen E. Rare disease terminology and definitions-a systematic global review: report of the ISPOR Rare Disease Special Interest Group. *Value Health*. 2015;18:906-914.
5. Moliner AM, Waligóra J. The European Union policy in the field of rare diseases. *Public Health Genomics*. 2013;16:268-277.
6. European Organisation for Rare Diseases. Rare diseases: understanding this public health priority. Eurordis. 2005.
7. Mazzucato M, Facchin P, Salamanca E, Angin C, Rath A. Orphacodes' use for the codification of rare diseases: results of the testing activity carried out within the rd-action framework. 9th European Conference on Rare Diseases & Orphan Products (ECRD Vienna 2018). *Orphanet J Rare Dis*. 2018;13(Suppl 2):167.
8. Koboldt DC, Steinberg KM, Larson DE, Wilson RK, Mardis ER. The next-generation sequencing revolution and its impact on genomics. *Cell*. 2013;155:27-38.
9. Baldovino S, Moliner AM, Taruscio D, Daina E, Roccatello D. Rare diseases in europe: from a wide to a local perspective. *Isr Med Assoc J*. 2016;18(6):359-363. 14.

10. Report EURORDIS 2005. European Conference on Rare Diseases. 2005. Luxembourg. Accessed August 26, 2021. https://www.eurordis.org/IMG/pdf/EN-ECRDtotal-2.pdf
11. Jimenez-Sanchez G, Childs B, Valle D. (2014). The effect of Mendelian disease on human health. In: Beaudet AL, Vogelstein B, Kinzler KW, eds. The online metabolic and molecular bases of inherited disea*se (Vol. 1)*. The McGraw-Hill Companies; 2001.
12. Peritore D, Trapani S, La Rocca V, et al. Rare disease patients as potential organ donors. *Transplant Proc*. 2020;52(5):1522-1524.
13. European Committee on Organ Transplantation. *Guide to the quality and safety of organs for transplantation*. EDQM 7th ed. 2018.
14. Herden U, Grabhorn E, Santer R, et al. Surgical aspects of liver transplantation and domino liver transplantation in maple syrup urine disease: analysis of 15 donor-recipient pairs. *Liver Transpl*. 2019;25:889-900.
15. Orphanet Report Series. Prevalence of rare diseases: bibliographic data. January 2019. Accessed August 26, 2021. http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf
16. Maldonado EM, Taha F, Rahman J, Rahman S. Systems biology approaches toward understanding primary mitochondrial diseases. *Front Genet*. 2019;10:19.
17. Rahman J, Rahman S. Mitochondrial medicine in the omics era. *Lancet*. 2018;391(10139):2560-2574.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Dallapiccola B, Moriconi S, Rugge M, et al. Organ donation from patients with a rare disease is often safe: the italian guidelines. *Clin Transplant*. 2022;36:e14769. https://doi.org/10.1111/ctr.14769