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Recommendations regarding screening, diagnosis, treatment, and clinical management of Chagas disease in Germany

1. Rationale and objectives

Chagas disease (CD) is a zoonosis caused by *Trypanosoma cruzi* infection and constitutes a one health concern. This neglected disease is currently endemic in 21 Latin American (LA) countries. It has spread globally due to increasing population mobility as well as several non-vectorial transmission routes (e.g., via mother-to-child, blood transfusion, transplantation, laboratory accidents, needle sharing among drug users, or ingestion of contaminated food) [WHO 2021]. Only few individuals at risk for or infected with *T. cruzi* seem to receive care according to current standards, even in high-income countries [Basile et al. 2011]. Many knowledge gaps as well as research and development priorities need to be addressed [Chatelain 2017]. The lack of specifically tailored recommendations or guidelines is an important risk factor for inadequate care [Manne et al. 2013]. A study published by Guggenbühl Noller et al. summarised available data on CD in Germany of nearly two decades [Guggenbühl Noller et al. 2020] and demonstrated that also in Germany only a small part of the population at risk received adequate care. Systematic screening and notification mechanisms are lacking, so that transmission routes remain uninterrupted.

Germany, together with all other member states of the WHO, endorsed the new road map for neglected tropical diseases 2021-2030 in November 2020 during the 73rd World Health Assembly [WHO 2020 (1) and (2)]. Objectives include the interruption of *T. cruzi* transmission pathways and a 75% coverage of the population eligible for antiparasitic treatment [WHO 2020 (2)]. Germany could achieve these aims by implementing appropriate national protocols. With these recommendations, under the lead of the German Society for Tropical Medicine, Travel Medicine, and Global Health e.V. (DTG; www.dtg.org), we aim to cover important aspects to improve the management of CD in the German public health care system. The recommendations are based on the current evidence available and authors' expert opinions. They cannot substitute individual clinical judgement and a regular update of this document needs to be performed.

2. Methodology

The Association of the Scientific Medical Societies in Germany ("Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften", AWMF) framework was used for the development of these recommendations [Muche-Borowski AWMF 2012]. AWMF represents Germany in the Council for International Organisations of Medical Sciences at WHO in Geneva, Switzerland. Recommendations presented here were classified as S1 ("recommendations by expert groups" using "consensus development in an informal procedure"). As the generation of this guideline has taken its start by convening representatives of relevant medical associations and entities in Germany, the authors decided to develop S1 level recommendations, with the aim to upgrade them in the future.

The group of authors consisted of at least one representative from all tertiary healthcare institutions offering routine CD testing in Germany, acknowledged physicians as well as scientists in the field, and representatives of relevant professional societies. The final document was externally reviewed by independent experts. It was approved by the participating professional societies and the steering committee of the DTG.

Conflicts of interest for group members were collected yearly via an online platform and evaluated by a suitable group member and the coordinator using standard procedures as outlined by the AWMF. In short, members reported no financial associations with companies relevant to these recommendations, the development of the recommendations was unfunded, and all members worked without payment or compensation. Original conflict of interest forms are available to the coordinator as well as the evaluating group member. A tabular summary can be found in the supplements.

A non-structured literature search was performed using Medline and the Cochrane register without language restrictions. Relevant documents and publications were identified and analysed for content. The foundation for each recommendation is stated in the respective paragraphs. Consent among group members was reached by video conference meetings and the circulation of the respective drafts and documents.

The strength of consensus was classified as strong consensus (>95% of participants), consensus (>75- 95% of participants), majority agreement (>50-75% of participants), and no consensus (≤50% of participants). Consensus generation was executed and documented using a digital voting tool.

3. Relevant and recent recommendations, guidelines, and reviews

The following list is a non-comprehensive overview but should give relevant sources of information that may be helpful for the reader.

Recommendations and Guidelines: Most existing recent consensus statements, recommendations and guidelines were developed for CD endemic territories with variable relevance, quality, and adaptability for the non-endemic German context. Of those, we want to highlight the guidelines for the diagnosis of suspected CD as well as trypanocidal treatment published by the Pan American Health Organisation (PAHO) [PAHO 2019] and other recent documents originating from or compiled for Argentina [Ministerio de Salud, Argentina 2018], Bolivia [Medicos sin Fronteras, España 2016], or Brazil [Dias et al. 2016].
Regarding CD in non-endemic European countries, several documents were developed for Spain, covering detection and management in primary healthcare [Bayón Rueda et al. 2009; Roca Saumell et al. 2015], screening measures [Velasco et al. 2020], HIV co-infection [Pérez-Molina et al. 2011], cardiomyopathy [Gascón et al. 2008], gastrointestinal disease [Pinazo et al. 2010], or organ and hematopoietic tissue transplantation [Pinazo et al. 2011].

Cochrane Analyses: A Cochrane analysis published in 2020 investigated the use of trypanocidal drugs for late-stage, symptomatic CD [Vallejo et al. 2020].

Systematic Reviews: Soriano-Arandes et al. published a review on control and management of congenital CD in non-endemic countries [Soriano-Arandes et al. 2016]. Requena-Méndez et al. studied health policies to control CD transmission in European countries [Requena-Méndez et al. 2014]. Bern et al. published a review on the evaluation and treatment of CD in the United States [Bern et al. 2007].

Unstructured Reviews: Abras et al. gave an overview on worldwide control and management of CD [Abras et al. 2022]. In 2019, Bern et al. published a comprehensive review about CD with a focus on the United States [Bern et al. 2019]. Kratz et al. gave an overview of the clinical and pharmacological profile of benznidazole for the treatment of CD [Kratz et al. 2018]. Angheben et al. gave a perspective on CD and blood transfusion medicine in non-endemic countries [Angheben et al. 2015].

4. Epidemiologic situation in Europe, with a focus on Germany

WHO estimates 6-7 million infected humans worldwide, mainly in LA countries [WHO 2021]. Data concerning CD in European countries and particularly in Germany are scarce, fragmentary, and outdated: recently it was estimated that roughly 4.6 million LA migrants live in Europe and that there may be between 68,000 to 122,000 undiagnosed cases of CD [Basile et al. 2011; Bayona-i-Carrasco et al. 2019; Navarro et al. 2022]. Ongoing migratory waves, together with other population movements, such as travellers or adoptions, would require frequent and regular data assessment to provide a more accurate picture [Bayona-i-Carrasco et al. 2019]. In 2020, a total of 140,565 immigrants from LA countries with CD endemic territories were officially registered in Germany [Statista 2021], leaving out undocumented migrants and migrants with European citizenship. The number of undocumented migrants is unknown, but they are likely to account for the highest CD prevalence rates and have limited or no access to health care [Basile et al. 2011; Jackson et al. 2010; Triandafyllidou 2009]. In 2015, a study estimated an overall CD prevalence of 4.2% among adult LA migrants in Europe [Requena-Méndez et al. 2015]. To date, only two studies on CD seroprevalence among LA migrants in Germany have been published: in 1997, Frank et al. described a seroprevalence of 2% among 100 LA migrants living in Berlin [Frank et al. 1997]. In 2017, Navarro et al. described a seroprevalence of 9.3% among 43 Munich citizens of Bolivian origin [Navarro et al. 2017]. In 2020, Guggenbühl Noller et al. published a retrospective study on CD testing in Germany from 2000-2018 and could identify a total of 81 diagnosed CD patients among 5,991 individuals tested within this time frame [Guggenbühl Noller et al. 2020]. For 814 out of 5,991 individuals nationality was available and only 16.0% of tested individuals with known nationality were from countries considered endemic. Only a fraction of identified CD patients received adequate care regarding antiparasitic treatment and clinical follow-up. Also a recent study from Spain reported a high index of underdiagnosis and undertreatment [Navarro et al. 2022].

5. Aspects on equity and social determinants

CD has been defined by WHO as being poverty-related and neglected [WHO 2021]. As such, the entity is suffering shortcomings in terms of the 10/90 gap, which means that only 10% of research and development are geared towards 90% of the global disease burden [Luchetti 2014]. CD is endemic in geographic regions of LA, with the highest national overall seroprevalence in Bolivia, a lower-middle-income-country [Bern et al. 2019; Hopkins et al. 2019; Medicos sin Fronteras, España 2016]. It afflicts mostly poorer, rural social strata, and transmission is associated with poor housing conditions, where the vectors, the triatominae (also known as kissing bugs), can reside in cracks of substandard walls (e.g., mud walls) and roofs (e.g., palm roofs). At the same time, the populations at risk suffer in general from limited access to health services. Long-term control strategies require information, education and communication strategies that are socio-economically and culturally adapted. Here, populations with limited access to information channels and reduced literacy are more likely to fail in benefiting from control strategies. In addition, control is dependent on community-based approaches and the commitment of the communities, as vector control requires ongoing community wide measures due to a high risk of re-infestation [Dell'Arciprete et al. 2014; Medicos sin Fronteras España 2016].

Due to its association with poverty, its chronicity, little knowledge about the disease and the difficulties in treatment, CD is also accompanied by self- and community stigma. In some countries, this stigma leads to an exclusion of CD positive patients from specific jobs, among other forms of social exclusion. Men are afflicted more frequently by CD, but at the same time are more difficult to reach through public health campaigns. However, due to vertical transmission (in LA some 8,000 annual cases of vertical transmission are estimated), women at childbearing age require more attention in control activities, while at the same time the bargaining power of women in many endemic countries is limited [Carlier et al. 2019; Medicos sin Fronteras, España 2016; Navarro et al. 2017; PAHO 2019].

The development of diagnostic tools and antiparasitic drugs are hampered. One key cause is a market failure: high demand due to disease burden in endemic regions does not sufficiently attract business and research activities because of the limited purchasing power of the afflicted poor social strata, which in turn leads to reduced market promises for drug developing companies. At the same time the affected societies need to prioritise health expenditures, and the populations at risk suffer from weak bargaining power, which leads to neglecting disease entities such as CD. As a result, diagnostic tools adapted to a low- and middle-income-setting have low diagnostic validity for active infection, and drugs used for treatment are compromised by side effects [Batista et al. 2019; WHO 2021].

Migrants from LA countries with endemic CD background who are reaching non-endemic countries remain mostly unserved in terms of CD. The reasons include a lack of awareness and limited or non-existent management capacities in the receiving countries. In addition, undocumented migrants have limited access to services as they are lacking coverage by health insurance. In the German context, undocumented migrants are also at risk of being prosecuted due to the requirements of German social services to notify to authorities patients without

entitlements of residence in those cases where the social services are requested to take over health care costs. Overall, rights of vulnerable and minority populations are frequently improperly addressed in the German public health system. Under-diagnosing, under-reporting, limited attention to conditions that are rare in the German local population, dragging policy development in volatile situations of migration, limited socio-cultural acceptability of services for migrants, and a limited human rights approach to health in a market-oriented health system are leading to a lack of proper attention [Guggenbühl Noller et al. 2020; Hotez & Gurwith 2011; Navarro et al. 2017].

6. Screening for *T. cruzi* infection

At the time of writing, no systematic screening measures for CD are implemented in Germany. When considering screening measures, one must consider many factors like individual benefit, cost-effectiveness, accessibility, available resources, potential harm, acceptance by those affected, and diagnostic reliability [Castillo-Riquelme 2017]. To date, the available evidence regarding CD screening measures is small to non-existent for non-endemic countries. Although disposing of methodologic difficulties, existing studies indicate a high economic burden resulting from CD and consider screening of at-risk individuals like LA migrants from endemic regions to be a cost-effective strategy [Imaz-Iglesia et al. 2015; Lee et al. 2013; Requena-Méndez et al. 2017; Sicuri et al. 2011]. Such screening measures remained cost-effective, even when the authors included large variations within their models. In addition, Germany, together with all other member states of WHO, endorsed the new road map for neglected tropical diseases 2021-2030 in the 73rd World Health Assembly in 2020 [WHO 2020 (1) and (2)]. The objectives include the verification of CD transmission interruption [WHO 2020 (2)]. Implementing appropriate national protocols could facilitate this and has been undertaken in other European countries [Angheben et al. 2015; Fernandez Turienzo et al. 2017; Requena-Méndez et al. 2014].

Figure 1: Chagas disease is currently classified to be endemic in 21 Latin American countries that are coloured in grey, namely Argentina, Belize, Bolivia (Plurinational State of), Brazil, Chile, Colombia, Costa Rica, Ecuador, El Salvador, French Guiana, Guatemala, Guyana, Honduras,

Mexico, Nicaragua, Panama, Paraguay, Peru, Suriname, Uruguay, and Venezuela (Bolivarian Republic of). The classification "originating from endemic areas" may be assessed on an individual basis, taking into consideration criteria like place of birth, nationality, or having spent childhood or adolescence in the respective endemic country.

Current evidence and expert opinions mostly favour serologic CD screening of the following individuals at risk originating from endemic areas or born to mothers with positive or unknown CD status from endemic areas: pregnant women, women of reproductive age, as well as blood or organ donors [Buekens et al. 2008; Carlier et al. 2011; ECDC 2014; Velasco 2020]. The EU directive 2006/17 on technical requirements for the donation, procurement and testing of human tissues and cells stipulates that suspicion of *T. cruzi* infection based on patient history requires CD testing [The Commission of European Communities 2006]. EU directive 2004/33 on technical requirements for blood and blood components states CD as a deferral criterion for blood donors [The Commission of European Communities 2004]. However, most individuals with CD in Europe are likely unaware of their infection status and thus, pre-transfusion questionnaires asking for known *T. cruzi* infection and deferring CD patients from donations have to be considered ineffective. In Europe, several countries including Belgium, France, Italy, Portugal, Spain, Sweden, Switzerland, and the United Kingdom conduct systematic screening for *T. cruzi* infection in at-risk blood donors. The 2009 recommendations by the Arbeitskreis Blut do not recommend serological screening of at-risk donors [Arbeitskreis Blut 2009]. However, based on more recent data and developments we recommend that at-risk blood donors should also be screened in Germany in order to interrupt transmission pathways of CD within Germany.

Table 1: Whom to screen for *T. cruzi* infection

Category	Population	Consensus strength
Screening recommended	**Pregnant women** who are ● originating from endemic areas or ● born to mothers from endemic areas with positive or unknown CD status	**Strong consensus**
	Women of reproductive age who are ● originating from endemic areas or ● born to mothers from endemic areas with positive or unknown CD status	**Strong consensus**
	Blood donors and organ donors/recipients who are ● originating from endemic areas or ● born to mothers from endemic areas with positive or unknown CD status	**Strong consensus**
Screening suggested	**Immunodeficient patients** or those **at risk of immunodeficiency** who are ● originating from endemic areas or ● born to mothers from endemic areas with positive or unknown CD status	**Strong consensus**

Screening decision on a case-by-case basis	**All individuals** who are ● originating from endemic areas or ● born to mothers from endemic areas with positive or unknown CD status	**Strong consensus**
	Asymptomatic individuals after long term residence in endemic areas based on infection risk profile	**Strong consensus**

Patients with immunodeficiency: Immunodeficiency is increasingly relevant, e.g., through neoplasms and/or immunosuppressant therapies. Several reports on CD reactivation in immunocompromised individuals have been published to date [Gray et al. 2018; Ringer et al. 2021] and other documents support screening in such situations [González-Ramos et al. 2017; Pinazo et al. 2013; Velasco et al. 2020]. Considering the high morbidity and mortality rate of insufficiently managed or even unnoticed CD re-activations, we suggest screening for CD of immunodeficient individuals or individuals at risk for immunodeficiency (e.g., prior to immunosuppressant treatment or in individuals living with HIV/AIDS) originating from endemic areas or born to mothers with a positive or unknown CD status from endemic areas.

The overall cost-benefit of serologic CD screening in asymptomatic individuals originating from endemic areas or born to mothers with a positive or unknown CD status from endemic areas as well as in individuals after long-term residence in endemic areas is complex to analyse. Prevalence as well as risks for infection may change over time and are associated with socio-economic factors, and data concerning this information for the relevant population in Germany is very scarce or even completely lacking [De Vito et al. 2015]. The relevance of CD for travel medicine in Germany is minor when looking into documented cases and tools for classification of high and low risk travellers are not available [Guggenbühl Noller et al. 2020]. Ongoing vector control measures reduce the risk of oral or vectorial *T. cruzi* transmission. Residence in endemic areas in poor dwelling conditions is a known risk factor and travellers visiting friends and relatives in endemic areas might have a higher risk of infection. Consumption of untreated juices (e.g., sugar cane, açaí) or wild game can convey the risk of oral *T. cruzi* transmission [Bern et al. 2020; WHO 2021]. In addition, as the individual benefit of etiologic treatment for asymptomatic CD patients depends on several factors (e.g., age, organ involvement) the eventual therapeutic decision requires a case-by-case assessment. Some potential costs associated with screening procedures have not been evaluated to date, such as the psychological impact of a CD diagnosis (e.g., anxiety and depression) or potential discrimination among individuals who were previously unaware of their infection status. We assume that most asymptomatic CD patients - especially children and adults < 50 years of age - benefit when tested positive from receiving appropriate (etiologic) treatment as well as clinical management following diagnosis [Lascano et al. 2022]. However, at least for elderly adults and individuals with advanced organ manifestations, this remains controversial: Current drugs available are hampered by side effects [Aldasoro et al. 2018; Malone et al. 2021]. In addition, appropriate clinical management is difficult to achieve, e.g., due to the knowledge gap among health care professionals in Germany, but also because verification of treatment success is difficult due to the absence of reliable biomarkers to this end. Considering these uncertainties, we suggest that screening for and information on CD should be offered and discussed in an

individualised fashion. Primary health care providers, paediatricians, gynaecologists, cardiologists, gastroenterologists, infectious disease specialists, and other suited health care professionals should use regular patient contacts to address this topic with at-risk individuals.

In Germany, at least five certified and partially accredited laboratories at the tertiary health care level offer suitable assays for CD screening and routine patient care (in Berlin, Bonn, Hamburg, Munich, Tübingen) [Guggenbühl, Noller et al. 2020]. Once a diagnosis is made, screening of family members (especially children where appropriate), social networks, and communities should be discussed and performed where indicated. In Germany, at-risk individuals without a recurrent risk to acquire CD (e.g., through future long-term stays in CD endemic countries) should only be screened once. As an example: if screening was negative during pregnancy, renewed screening during subsequent pregnancies is unnecessary without renewed risk for infection. We suggest that screening tests should be covered by regular health insurance, considering the risk, benefit, and the probable cost-effectiveness of those measures; however, in a communication with the working group of this recommendation document, the Kassenärztliche Bundesvereinigung as the federal representative of the German statutory health insurances, did not ascertain an a-priori coverage of such screening measures. An official statement by the Gemeinsamer Bundesausschuss (GBA), the legal body defining health services covered by the statutory health insurance is still pending [personal communication].

7. Diagnosis of *T. cruzi* infection

The parasite *T. cruzi* can exist intra- and extracellularly in different forms. Diagnostics need to be chosen based on patient characteristics (e.g., age or immune status) and disease stage (e.g., acute, chronic, congenital, or reactivated). Several diagnostic methodologies for direct as well as indirect parasite detection exist and are described below.

Table 2: How to diagnose chronic CD in non-immunocompromised individuals aged ≥ 1 year

Situation	Population	Consensus strength
Primary testing	**Two different serological tests using different methods/antigens**	**Strong consensus**
Confirmatory testing in case of conflicting or inconclusive primary test results	**An immediate third serological test or**	**Consensus**
	Repetition of two different serological tests after three months	**Strong consensus**

Diagnostic Methods: Direct parasite detection in blood using microscopy is considered the gold standard for many parasitic diseases. Due to the variability of parasitaemia, repetitive blood sampling may be useful. Direct microscopical identification of *T. cruzi* trypomastigotes in blood can almost only be achieved in the acute infection phase, in the new-born, or during reactivation. The likelihood of detection may be increased by concentration techniques (e.g., thick films, buffy coat method, or Strout method). Staining (e.g., Giemsa) can facilitate morphologic characterisation and differential diagnoses (e.g., malaria). During the chronic infection phase, direct parasite detection in blood by microscopy is usually not possible due to an extremely low or absent parasitaemia. However, *T. cruzi* amastigotes can potentially be detected in biopsy material of any affected tissue (e.g., muscle, liver, spleen, lymph nodes). Trypomastigotes may also be microscopically detected in cerebrospinal fluid when meningo-encephalitis is present. Microscopy identification is highly dependent on the availability of equipment, resources (e.g., time available for examination), and experience and skills of the examining staff. Direct parasite detection via qualitative or quantitative PCR is more sensitive than microscopy. PCR can be used in patient care and clinical trials as a surrogate marker for treatment success or to quantify parasite load [Seiringer et al. 2017]. A confirmed positive PCR after completing antiparasitic treatment indicates treatment failure. Additionally, PCR methods and the Shed Acute Phase Antigen (SAPA) assay can be useful to determine possible congenital infections where transfer of antibodies from mother to child impedes serological methods [Castro-Sesquen et al. 2021; Mallimaci et al. 2010; Piron et al. 2007], to detect recently acquired infections [Grauert et al. 1993], to monitor for potential reactivations, and to investigate possible cross-reactivity or inconsistent serological test results [Gomes et al. 2009; Wincker et al. 1994; Marcon et al. 2002]. Genotyping is currently only used for

epidemiologic or research purposes, as genotypes currently do not influence the clinical management of CD patients. Direct parasite detection via antigen test, blood culture or xenodiagnosis are possible, but not established for patient care in Germany as they are complex, time-consuming, or less reliable than serological methods and PCR testing.

Indirect detection mainly depends on serological tests that detect IgG antibodies against *T. cruzi* specific conserved epitopes and is used for screening (e.g., blood donors, organ donors, subjects for epidemiologic studies, at-risk individuals) and the diagnosis of suspected CD. Available tests have considerably increased in quality and can reach sensitivities of up to 100% with specificities of 97-99% [Abras et al. 2016; Flores-Chavez et al. 2018]. Commercially available *T. cruzi* specific antibody tests include enzyme-linked immunosorbent assays (ELISA), hemagglutination-inhibition assays (HAI), immunochromatographic tests (ICT), indirect immunofluorescence tests (IIFT), chemiluminescent microparticle immunoassays (CMIA), western blots (WB), and particle-agglutination tests (PA). Immunocomplexes (e.g., by rheumatologic diseases) or cross-reactivity caused by other protozoal infections (e.g., *Leishmania spec.*, *Trypanosoma rangeli*) may lead to false-positive results. Two different serological tests should be used for CD diagnosis. It is best to choose one test with high sensitivity and one with high specificity that use different methods and antigens. In case of discordance of results, a third serological test should be performed, or serological testing should be repeated after 3 months. Where available PCR can be considered, however, we would like to point out that PCR has rather confirmatory qualities and is not suitable to rule out infection. Together with PCR, serological tests are being used to measure treatment success after antiparasitic treatment. However, it must be considered that after successful treatment serological results often are not recorded to revert to negative. Depending on infection phase, duration, and patient characteristics it may take months (e.g., congenital infections), years (acute and/or recent chronic infections), or decades (chronic infections of longer duration). It is also possible that the antibodies stay positive for a lifetime, without this having a clear correlation with the patient's prognosis.Our recommendation to diagnose suspected chronic CD by using two different serological tests follows the most recent recommendations by PAHO [PAHO 2019]: For their guidelines, PAHO considered all available technologies, relevant studies available, and tried to calculate associated benefits and risks. In Germany, the lack of reliable data on at-risk individuals as well as the respective overall prevalence rates impede more detailed calculations specific for Germany. For the period after the structured literature review by PAHO, we did not find new evidence that would justify a change of their recommendations.

Diagnostic Capacities in Germany: In Germany, five centres offering CD diagnostics for routine patient care in officially certified laboratories at tertiary health care level were identified [Guggenbühl Noller et al. 2020]:

Table 3: Tertiary level facilities in Germany offering CD diagnostics

City	Facility	Testing portfolio

Berlin	**Institute of Tropical Medicine and International Health, Charité - Universitätsmedizin**	**Microscopy, in-house ELISA**
Bonn	**Institute for Medical Microbiology, Immunology and Parasitology, University Hospital Bonn**	**Microscopy, commercial ELISA, commercial Westernblot**
Hamburg	**Bernhard Nocht Institute for Tropical Medicine**	**Microscopy, in-house ELISA, in-house IIFT, qualitative in-house PCR**
Munich	**Division of Tropical Medicine and Infectious Diseases, University Hospital, LMU**	**Microscopy, in-house ELISA, in-house IIFT, qualitative in-house PCR followed by commercially available quantitative PCR if positive**
Tübingen	**Institute of Tropical Medicine, Medical Department, University Hospital**	**Microscopy, in-house IIFT**

We would like to point out that in addition there are other institutions that offer direct detection by microscopy and privately run laboratories offering CD testing. However, we did not include a systematic search on testing capacities in private laboratories. We recommend contacting the respective laboratories before obtaining and sending specimen for analyses other than serological testing. Contact details as well as information concerning the shipment can be found on their respective web pages. Costs of diagnostic testing for CD during routine patient care in individuals with suspected CD should be covered by regular health care insurance.

8. Trypanocidal treatment

Table 4: Whom to offer trypanocidal treatment		
Category	**Population**	**Consensus strength**
Trypanocidal treatment recommended	Patients with acute *T. cruzi* infection	**Strong consensus**
	Patients with congenital *T. cruzi* infection	**Strong consensus**
	Patients with *T. cruzi* reactivation	**Strong consensus**
	Patients < 18 years of age with chronic *T. cruzi* infection	**Strong consensus**
	Non-pregnant women of childbearing age with chronic *T. cruzi* infection	**Strong consensus**
Trypanocidal treatment suggested	Patients 18-50 years of age with chronic *T. cruzi* infection without specific organ damage	**Strong consensus**
Trypanocidal treatment decision on a case-by-case basis	Patients > 50 years of age with chronic *T. cruzi* infection without specific organ damage	**Consensus**
	Patients ≥ 18 years of age with specific organ damage	**Strong consensus**

Clinical course and definition of terms: CD can be classified in different phases [WHO 2021]. The first 1-3 months after infection are called the acute phase. Most patients develop high parasitaemia and symptoms are mostly mild and unspecific but can also be completely absent or severe. After this, patients enter the chronic phase. Parasitaemia is low or absent, parasites are mostly "hiding" in organ tissues like muscle cells of the heart or the digestive tract. After an asymptomatic period of variable duration, around 30% of those chronically infected develop cardiac and 10% digestive functional impairment, neurological or mixed manifestations are also possible. This specific organ damage can cause substantial impairment and eventually lead to death. Mainly during immunodeficiency, CD can be reactivated with renewed parasitaemia and is associated with high morbidity and mortality. Congenital CD defines the infection of a new-born during pregnancy or childbirth by her infected mother.

Trypanocidal therapy: Trypanocidal therapy aims to eliminate *T. cruzi*, reduce *T. cruzi* associated morbidity as well as mortality, and to prevent congenital transmission. Until now, benznidazole (BNZ) and nifurtimox (NFX) are the only trypanocidal drugs available. Currently, only a small fraction of CD patients (maybe even < 1%) receives adequate care and therapy [Guggenbühl Noller et al. 2020; Pecoul et al. 2016; Ribeiro et al. 2009]. Among others, this is due to lack of diagnosis, missing knowledge among healthcare professionals, lack of access to healthcare, concerns about adverse events of the medication and regulatory and structural health system problems.

Researchers look at improved regimens and combinations of BNZ with other substances to increase the efficacy and safety of BNZ therapy. However, none of those substances are used in clinical practice so far [Kratz et al. 2018]. Administering antiparasitic treatment in the primary health care and outpatient setting is feasible and increases adherence as well as safety and facilitates continuous monitoring. Patient characteristics like comorbidities, concomitant medications and contraindications need to be considered when considering trypanocidal treatment. In general, a thorough clinical workup, procurement of medication and overall management (see section 9 “Management of CD patients" below) regarding CD should be ensured, especially for populations that are disadvantaged in terms of access, e.g., unregistered migrants or individuals with language barriers.

Women of childbearing age and in pregnancy: A pregnancy test should be obtained in women of childbearing age before treatment initiation and safe contraception should be practiced during treatment and thereafter (5 days after last dose for BNZ; 6 months after last dose for NFX) [Mayoclinic Drugs and Supplements 2022]. All patients should be regularly monitored before and during treatment including risk history, physical examination, and laboratory tests, as outlined in recent guidelines and publications [Bern et al. 2007; see Figure 2].

Drug related adverse events: Potential adverse events should be managed regarding type and severity. Only a minority of adverse events are classified as serious, leading to discontinuation of treatment. Children tolerate both treatment options better than adults, but even less than 10% of elderly patients will discontinue BNZ treatment with proper management [Morillo et al. 2015; Kratz et al. 2018]. Several guidelines and publications suggest strategies for the management of adverse events, which may involve a temporary reduction of the daily doses or suspension of treatment. In addition, recent studies suggest that even low or short dosing of BNZ might have similar efficacy when compared to the standard regimen, which might lead to beneficial outcomes even when treatment discontinuation was necessary [Castro Eiro et al. 2021; Torrico et al. 2018; Torrico et al. 2021]. For instance, Argentinian guidelines consider BNZ treatment of a duration of at least 30 days as complete [Ministerio de Salud, Argentina 2018].

Drug procurement: Although BNZ and NFX are included in the WHO's list of essential medicines, they lack regulatory approval and registration in many countries, including Germany. This and the fact that information concerning their supply chains is not readily available, negatively impacts treatment access [Manne et al. 2013]. To receive BNZ or NFX from WHO, medical doctors must complete the WHO request form (see appendix) and send it via email attachment to the respective WHO desk (at the time of writing: Marilyne Vonlanthen (vonlanthenm@who.int) with Rosa Maria Perea Ibañez (perear@who.int) and Pedro Albajar Viñas (albajarvinasp@who.int) in carbon copy). For each dispatch of medicine sent by rapid courier, WHO attaches necessary certificates (compound analyses and Good Manufacturing Practice statement). In Germany, medical doctors are obliged to prescribe both drugs in a situation of a so-called individual healing attempt, a condition which is poorly regulated and for which the treating physician needs to ask informed consent from the patient [Verband Forschender Arzneimittelhersteller 2022].

Risk and benefit considerations for etiological treatment: An international consensus exists for the treatment recommendations above: There is agreement that the high parasitological cure rate and the prevention of specific organ damage, severe complications, and congenital transmission as primary prevention outweigh negative aspects of trypanocidal treatment (e.g., severe side effects or stigmatisation). Outcomes like treatment interruption due to adverse effects, surrogate markers (absence of parasitaemia and conversion of a previously positive serological test result to negative), functional cardiac impairment, and death have been investigated. However, research and management are severely affected by the lack of a reliable biomarker promptly proving treatment success and thus monitoring of cure. Overall confidence in the body of evidence is low. Still, we believe that most patients benefit from antiparasitic treatment through reduction of the parasite burden and clinically relevant outcomes (e.g., prevention of specific organ damage or slower disease progression). For some patient groups the potential benefits could be considerably greater than for others: younger patients (18-50 years) without or with early gastrointestinal or heart disease might benefit in the long term, as well as more recent chronic infections [Viotti et al. 2005] when treatment is being administered as soon as possible to delay or prevent disease progression [Bern et al. 2019; Morillo et al. 2015; Pecoul et al. 2016]. We are aware that some patients as well as physicians may give more weight to the potential adverse effects of trypanocidal treatment than to potential benefits. Patients at risk for or with compromised immunity (e.g., with HIV coinfection, other potentially immunosuppressant diseases, or before starting immunosuppressive treatments) could additionally benefit from trypanocidal treatment by the prevention of flare-ups and the potentially severe consequences thereof [Bern 2012]. Some physicians and immunocompromised patients, however, may opt to monitor the infection closely and only treat for *T. cruzi* infection in the event of reactivation. Trypanocidal treatment in chronic CD patients with advanced functional cardiac impairment does not show clear benefits and thus is currently not recommended or suggested [Morillo et al. 2015; PAHO 2019; Vallejo et al. 2020]; unless the patient is going to be a transplant candidate, since treatment may be considered to prevent reactivation, as mentioned above. In addition to the recommendations, we suggest offering trypanocidal treatment to all patients 18-50 years with chronic *T. cruzi* infection and without specific organ damage. For patients > 50 years without specific organ damage or patients ≥ 18 years with specific organ damage, trypanocidal treatment needs to be discussed on a case-by-case basis and in an individual decision-making process.

Choice of etiological drugs and posology: Considering tolerance, efficacy, and treatment durations, we suggest using BNZ as first-line treatment in CD patients [Müller Kratz et al. 2018; Torrico et al. 2018; Torrico et al. 2021]. We suggest using NFX as second line treatment. It can be considered when BNZ is unavailable, severe side effects preclude continuation of BNZ and either treatment duration was very short (< 30 days) or there is evidence of treatment failure.

Table 5: Recommended trypanocidal treatments

Trypanocidal drug	**Regimen priority line**	**Consensus strength**

Benznidazole (BNZ)	First line treatment (dosing below)	**Strong consensus**
Nifurtimox (NFX)	Second line treatment (dosing below)	**Strong consensus**

Table 6: Posology for benznidazole (first line treatment)

Situation	Body weight	Dosing scheme
Acute infection	≤ 40 kg	7.5-10 mg/kg body weight divided in 2-3 daily doses (max. 300mg daily) Duration: 60 days
	> 40 kg	5-7 mg/kg body weight divided in 2-3 daily doses (max. 300mg daily*) Duration: 60 days*
Congenital infection		10 mg/kg body weight divided in 2-3 daily doses Duration: 60 days
Chronic infection	≤ 40 kg	7.5 mg/kg body weight divided in 2-3 daily doses Duration: 60 days
	> 40 kg	5 mg/kg body weight divided in 2-3 daily doses (max. 300mg daily*) Duration: 60 days*

*Several dosing schemes for BNZ are in circulation. It is known that some adverse effects are related to the daily doses given. Thus, many experts and guidelines recommend a maximum daily dose of 300mg [Dias et al. 2016; Ministerio de Salud Pública y Bienestar Social, Paraguay 2021]. In this case, many recommend to extend treatment duration >60 days in order to reach or get close to the calculated total drug dose calculated for 60 days [Dias et al. 2016; Ministerio de Salud Pública y Bienestar Social, Paraguay 2021]. Some experts try to help very obese patients to lose weight before starting antitrypanocidal treatment. In any case, close BNZ treatment monitoring is fundamental. If there are any doubts or problems in regard to antitrypanocidal treatment, especially in patients >60kg body weight, specialised centers with treatment experience should be contacted and involved (see centers mentioned in Table 3 and dtg.org).

Table 7: Posology for nifurtimox (second line treatment)

Situation	Bodyweight	Dosing scheme as recommended by WHO
Acute infection	≤ 40 kg	10-15 mg/kg body weight divided in 2-3 daily doses Duration: 60 days
	> 40 kg	8-10 mg/kg body weight divided in 2-3 daily doses Duration: 60 days
Congenital infection		10-15 mg/kg body weight divided in 2-3 daily doses Duration: 60 days
Chronic	≤ 40 kg	10-15 mg/kg body weight divided in 2-3 daily doses Duration: 60 days

infection	> 40 kg	8-10 mg/kg body weight divided in 2-3 daily doses Duration: 60 days

9. Management of CD patients

Current consensus recommends the integrated management of CD patients in the primary healthcare setting and a reference network for up- and down-referral where necessary. Comprehensive longitudinal management of CD is necessary to account for all patient characteristics and clinical presentations. Existing clinical guidelines need to be adjusted to local realities to use all possible diagnostic and therapeutic opportunities. Management of CD should not interfere with the management of other diseases and comorbidities. During immunosuppression patients should be closely monitored for possible reactivations. No universal recommendations exist to assess treatment success. Patients should be advised not to donate blood and consult their physician before any donation of organs or tissues. If women undergo treatment, pregnancy should be prevented until after completion of treatment (see also above section 8 “Trypanocidal treatment”).

Organ involvement: To detect specific organ damage, initial tests should at least include regular medical evaluation (history, physical examination), an ECG with 30-second rhythm strip, a chest x-ray, and an echocardiography. If the initial evaluation was unremarkable, we recommend performing an annual medical evaluation and ECG with a 30-second rhythm strip. Once organ manifestations are suspected or detected, the respective specialists (infectious diseases, cardiologists, gastroenterologists, neurologists, etc.) should be involved in patient management. The risk of serious cardiac events seems comparable to that of the general population if no cardiomyopathy is detected. Once functional impairment of the left or right cardiac ventricle is present, progression can be considerably faster than in cases of other aetiologies: cases with advanced Chagas cardiomyopathy are at high risk of death and require thorough immediate and follow-up evaluation. Echocardiography may be used to determine left ventricular dysfunction and cardiac magnetic resonance tomography (cMR) may be of help to identify regions with scar formation based on late gadolinium enhancement, usually focused on the epicardial aspect of the ventricular wall. If indicated, antiarrhythmic drugs, catheter ablation, implantation of cardioverter-defibrillator devices as per current cardiology guidelines should be used. Heart transplantation should be taken into consideration where appropriate (see next section). Particularly in terms of the cardiovascular forms of the disease, deaths occur frequently due to delayed interventions. Primary or secondary prophylactic ICD implantation should be considered based on current guideline recommendations. Overall management should consider potential cultural and language barriers, legal status, as well as coverage of costs (health insurance). If problems arise regarding the management of CD patients, specialised centres in tropical medicine should be contacted early-on (see www.dtg.org for contact details).

Table 8: Patient evaluation and secondary prevention

Situation	**Evaluation components**	**Consensus strength**
Baseline evaluation in asymptomatic patients	Medical history, full clinical examination, ECG with 30-second rhythm strip, chest X-ray, and echocardiography	**Strong consensus**

Follow-up in asymptomatic and immunocompetent patients without specific organ damage	Annual clinical examination and ECG with 30-second rhythm strip	**Strong consensus**
Follow-up with specific organ damage	Interdisciplinary patient management by experts in tropical medicine/infectious diseases as well as specialists in the respective field of organ manifestation (e.g. cardiology, gastroenterology, bowel surgery).	**Strong consensus**

Heart transplantation: Heart transplantation may be required in patients with advanced Chagas cardiomyopathy. The usual indications apply here (considerable limitations of physical activity and quality of life due to cardiac insufficiency). However, in case of Chagas cardiomyopathy, the possibility of faster progression must be considered, which makes a rapid evaluation and connection to a transplantation centre necessary. This is supported by data from USA and LA [Abuhab et al. 2013; Bestetti and Theodoropoulos 2009] which show increased mortality on a heart transplant waiting list in addition to a more rapid disease progression. At the same time, the survival rates of patients after transplantation are higher [Bocchi and Fiorelli 2001]. These circumstances must be considered when determining the indication for transplantation. Thus, a patient with Chagas cardiomyopathy should be presented early to an experienced cardiac transplant centre. The following patient groups are particularly at risk of rapid disease progression:

- Left ventricular ejection fraction < 30% [Bestetti and Theodoropoulos 2009]
- Persistent stress restriction NYHA III - IV [Bestetti and Theodoropoulos 2009]
- Malignant ventricular arrhythmia with ICD indication; the number of shocks delivered is an independent predictor of high mortality [Cardinalli et al. 2007]

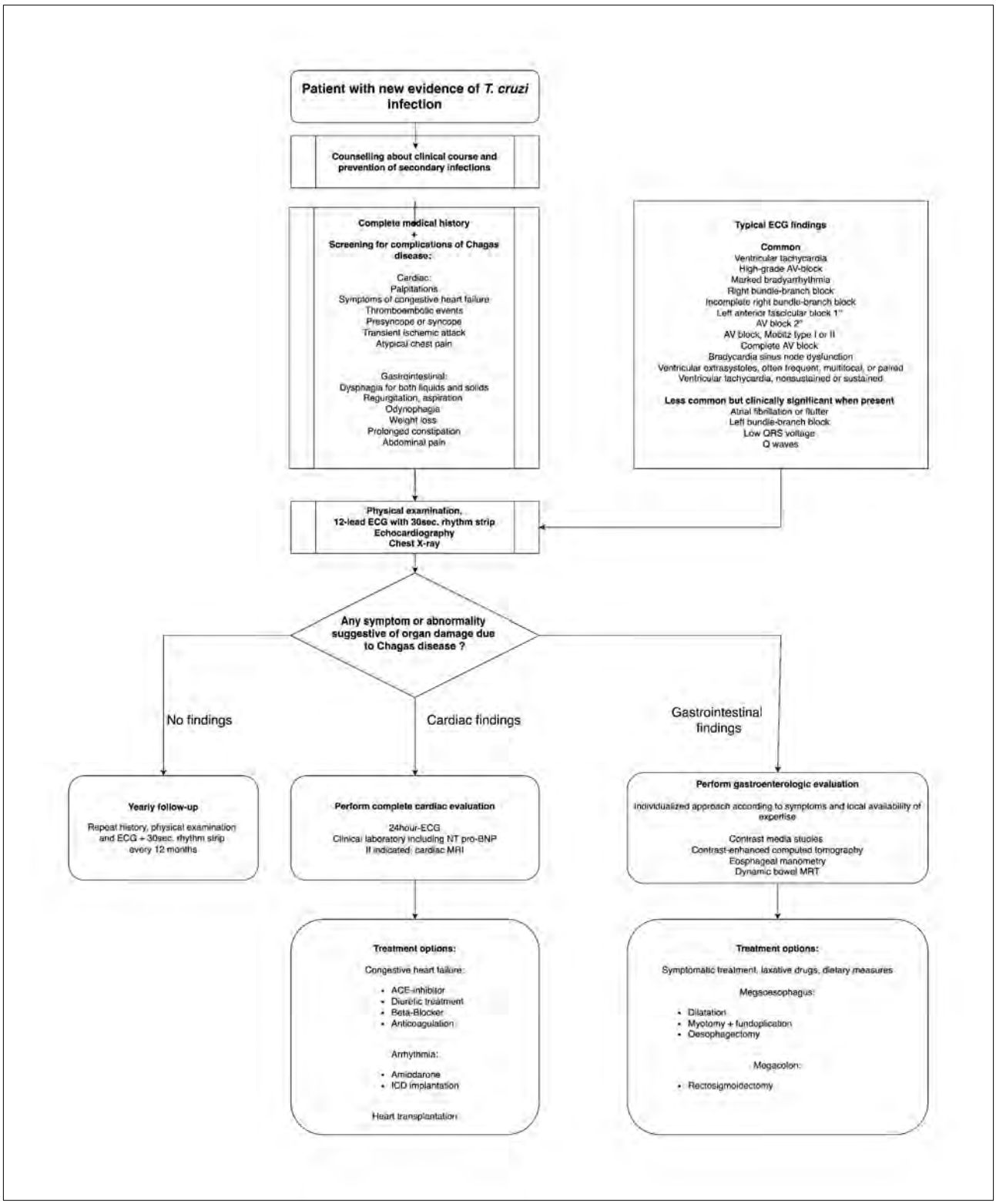

Figure 2: Clinical evaluation and management of patients newly diagnosed with CD, partially adapted from Bern et al. [Bern et al. 2007]. Please note, this figure does not include trypanocidal treatment. For recommendations regarding trypanocidal treatment please see Table 4.

Pregnant women and their offspring: Women of childbearing age should be counselled about the possible transmission risk to their new-born. The rate of mother-to-child transmission without previous trypanocidal treatment is reported to be about 5% (with a wide range varying according

to different study areas), with transmission rates on the lower side in non-endemic areas [Howard et al. 2014; Santana et al. 2020; PAHO 2019; Carlier et al. 2015]. Early treatment of congenitally infected children has high success rates; therefore, screening should be offered to all pregnant women at risk [Carlier et al. 2019]. All infants born to women who tested positive for CD should also be tested for CD. As maternal antibodies are transferred to the child during pregnancy, serological testing methods are not appropriate to diagnose congenital infection in the first months of life. We recommend performing PCR testing in the first week after delivery before discharge from the maternity clinic (not from cord blood). If the PCR result is negative, we recommend another PCR at one to two months of age (period corresponding to the most likely peak of parasitaemia) [Bua et al. 2013; Livingston 2021]. If this again is negative, we recommend serological testing at >10 months of age (after elimination of maternal antibodies that have been transferred trans-placentally [Carlier et al. 2019]. If the index infant's older siblings have not been tested previously, they should also be offered testing. Breastfeeding in chronically infected mothers should be encouraged, as the benefits of breastfeeding likely outweigh the very low risk of transmission through breast milk. The risk of transmission may be higher if there is bleeding from the nipples or open lesions, and women may choose to discard the breast milk if there is active bleeding. Literature supports breastfeeding in *T. cruzi* infected mothers [Bittencourt et al. 1988; González-Tomé et al. 2013; Norman and López-Vélez 2013]. Because of limited data on safety, treatment of the mother should be delayed until breastfeeding is terminated. However, levels of both BNZ and NFX in breastmilk are low. All clinical evaluation of the breastfed babies suggests that maternal BNZ treatment for Chagas disease during breastfeeding is unlikely to present a risk for the breastfed infant [García-Bournissen et al. 2010, García-Bournissen et al. 2015, Vela-Bahena et al. 2015]. In addition, possible adverse events of antiparasitic treatment may lead to interruption of breastfeeding.

10. Prevention

Preventive measures in Germany should focus on (i) the prevention of non-vectorial transmission to prevent new CD cases (e.g., screening of blood and organ donors with a relevant migration history as indicated above) and (ii) the timely diagnosis, treatment, as well as appropriate clinical management of chronically infected individuals, to prevent e.g., vertical transmission and to ensure secondary and tertiary prevention. Even if cure is not achieved, clinical progression might be prevented, morbidity and mortality reduced, healthy years of life maximised, and the social and economic burden decreased.

Counselling of expatriates bound for LA should include mentioning CD and avoiding vectorial and non-vectorial transmission. Training in travel medicine, especially if in an occupational context, should include an introduction to the screening procedures after return as outlined above.

On an international health scale German development cooperation, e.g., by the German Ministry of Economic Cooperation and Development, should consider including systematic CD control measures in its projects in CD endemic countries. This would correspond to an element of primary prevention in potentially future migrants to Europe and Germany.

11. Implementation and dissemination

The implementation and dissemination strategy should provide information, communication, and education to health service providers, public health authorities, policy makers, and at-risk groups. The guidelines will be shared with all relevant medical societies in a digital format, to stimulate further communication with the member physicians of these societies. The author group is planning to place presentations on the guidelines in scientific and medical educational events, such as symposia of relevant medical societies. In addition, publications in scientific journals, and as a common tool of communication in the Deutsches Ärzteblatt, are scheduled.

At-risk groups will be addressed through media communications (including social media), and by contacting civil society groups that work with migrant populations, such as humanitarian organisations.

Additional measures, such as formalised training interventions, digital decision-making support for physicians, or m-health tools, would be favourable, but are beyond the capacity of the steering group.

12. Surveillance, monitoring, and evaluation

The authors of these recommendations are suggesting the establishment of a national database for CD, to provide an instrument of surveillance and monitoring. This would also corroborate advocacy vis-à-vis policy makers. However, we are aware that this is resource-intensive, and beyond the capacity of the steering group. Consequently, repeated sentinel surveillance studies should be conducted.

Primarily, surveillance should be a responsibility of national and state health authorities. But academia can support in a situation where a national public health intervention is unlikely. We suggest supporting research groups on CD to conceive annual facility-based data collections, and to complement by five-yearly longitudinal analyses. These studies need to be provided with sufficient resources in terms of research funding.

13. Updating

This document as S1 recommendation is meant as a starting point, to provide basic guidance and information. The authors of these guidelines are committed to maintain a standing steering group to monitor for further developments and publications. Further research and attention may then lead to an upgrade in the level of the guidelines. We are planning to convene within a time frame of five years, to evaluate need and capacity to update and upscale. The development and validation of a score and a digital tool for the evaluation of infection risk should be envisioned.

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Participation agreed, withdrawn for reasons that are not associated with these S1 CD recommendations: German Society of Epidemiology (representative: Krumkamp, Ralf)

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