An Overview of the Trajectory of Brazilian Individuals with 22q11.2 Deletion Syndrome Until Diagnosis.

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Research

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Abstract

Background: 22q11.2 Deletion Syndrome (22q11.2DS) is a rare disease that has as an important characteristic the clinical heterogeneity. The diversity of organs, regions, and systems of the body that can be affected requires periodic updating of health professionals so that they can recognize this clinical signs as belonging to 22q11.2DS. Updated health professionals are equally important for the appropriate and timely establishment of clinical management for individuals with a positive diagnosis. In this context, this article aimed to map and analyse the access to health care for individuals with 22q11.2DS until the moment of diagnosis.

Results: We analysed clinical data of 111 individuals with 22q11.2DS registered in the Brazilian Database on Craniofacial Anomalies (BDCA) from 2008 to 2020. In this study, individuals were diagnosed with a median age of 9 years (mean = 9.7 years). Before genetic investigation, they accessed 68.75% of the international recommended evaluations available at BDCA. Recurrent 22q11.2DS clinical manifestations as delayed neuropsychomotor development, lip and/or palate defects, cardiac malformation and/or hematological/immunological alteration co-occurred in at least 72.06% of individuals. Cardiac malformation was the only clinical alteration that led to a lower median diagnostic age, corresponding to 6.5 years of age with a cardiac malformation versus 11 years of age without a cardiac malformation ($p = 0.0006$).

Conclusions: In Brazil, 22q11.2 DS is under recognized and early diagnosis and management of affected individuals are still a distant reality. In this sense, the identification followed by the correction of obstacles that do not allow this reality are essential to increase life expectancy and improve the quality of life of these individuals in Brazil

Background

The 22q11.2 Deletion Syndrome (22q11.2DS) is a rare disease of genetic origin. It has an estimated incidence among different populations of 1:3000 to 1:6000 live births, which ranks it as the most frequent microdeletion in humans (1, 2).

The first and most frequent clinical manifestations in 22q11.2DS are the dysmorphic features, hypocalcemia and/or hypoparathyroidism, delayed neuropsychomotor development (NPMDD), heart and lip/palate defects. From the first year of life until preadolescence delayed speech acquisition or nasal voice, behavioural alterations like anxiety, attention deficit, hyperactivity, socialization problems and learning difficulties are also common. During adolescence and adulthood, neuropsychiatric disorders such as bipolar disorder, schizophrenia, anxiety, and intellectual disability are recurrent and can interfere or limit their social insertion (3–5).

Although there are more common alterations in each age group, studies associated over 180 clinical manifestations with 22q11.2DS (2, 6). Clinical heterogeneity makes it difficult to understand insidious signs and symptoms as belonging to a single phenotype, which increases the complexity of the suspicion

and diagnosis of 22q11.2DS. In Brazil, 10 years is the average diagnosis age for individuals with this syndrome (7, 8).

Delay in diagnosis impairs the institution of health interventions at an appropriate age. The management should be personalized, based on the clinical changes and severity of the symptoms observed. To handle the planning of this management there are guidelines for clinical and laboratory investigations for the moment of diagnosis and post-diagnosis follow-up in the different age groups (3).

Recommended assessments to establish individual health care and management include pediatric/clinical, cardiac, nasopharyngeal, immunological, hematological, endocrinological evaluations, renal, hearing, ophthalmic, orthopedic, dental, psychopedagogical, psychiatric and genetic counseling. Add up gynecological evaluation, sex education and genetic orientation of the proband in adolescence and adulthood (4, 9).

In Brazil, the Comprehensive Care Policy for People with Rare Diseases (PAIPDR - Ordinance GM/MS nº 199/2014) (10), within the Unified Health System (SUS), regulates the treatment of individuals with rare diseases. In this, there are currently 17 enabled reference centers (11). Therefore, considering the difficult suspicion of 22q11.2DS, the Brazilian population and the territorial extension, there are obstacles to access confirmatory tests, genetic orientation and clinical management (12). Within this framework, the notification of rare diseases is not compulsory in the country (13), making impossible a health situation analysis of the population with 22q11.2DS, based on data such as prevalence, clinical management, health needs and life expectancy. Additionally, there are no guidelines defined by the Ministry of Health for health care of this population group.

Brazil's Craniofacial Project (BCFP) is a voluntary, multicenter and inter-institutional initiative. BCFP aims to improve health care for individuals with craniofacial alterations from the production of scientific evidence to subsidize public policies (14). Since 2006, BCFP has acted in the development of strategies to increment the diagnosis of 22q11.2DS, such as refinement of the common phenotype and registration of clinical follow-ups in the Brazilian Database on Craniofacial Anomalies (BDCA) (8, 15). Furthermore, BCFP has drawn up a 22q11.2DS clinical management guide in Portuguese (5).

The investment in training health professionals, continuous and proper clinical management, made possible by the early 22q11.2 DS diagnosis, potentiates the reduction of morbidity and mortality, the increase in life expectancy, the reduction of treatment expenses and helps caregivers prepare for the natural evolution of the syndrome (16–18).

Based on the information of individuals with 22q11.2DS recorded in the BDCA, the present study aimed to characterize the clinical investigation carried out until the diagnostic conclusion and identify the factors that interfered in this investigation. The knowledge of this trajectory allows recognizing and subsidizing the enhancement and targeting of public policies to improve the suspicion of 22q11.2DS and the access to adequate health management.

Methods

The Ethics Committee of the State University of Campinas approved this study (CAAE: 2477419.1.0000.5404) and all participants or their guardians signed the Informed Consent Form.

We analysed primary data of 111 individuals with 22q11.2DS, from BDCA, linked to BCFP (14, 19). This data was collected from 2008 to 2020.

Diagnosis of 22q11.2DS

All individuals taking part in this study presented positive results for typical deletion in region q11.2 of chromosome 22. BCFP performed diagnostic exams of all cases and without cost to the family. The diagnostic methods used were FISH and/or MLPA and CMA, according to the research projects through the years. The age of diagnosis ranged from 0 to 33 years and is equivalent to the time of access to genetic research. Individuals diagnosed with less than 1 year of age had their age of diagnosis classified as 0.

Clinical aspects and health interventions

The time of diagnostic test access is equivalent to the registration time in BDCA and the collection of data on clinical aspects and health interventions. Therefore, the age of diagnosis is the same as that of genetic counseling of the parents.

Based on the international recommendations of clinical management at the time of diagnosis of 22q11.2DS, the assessments available in the BDCA to analyze the therapeutic itinerary until the diagnosis were: a) cardiac, b) nasopharyngeal, c) hearing; d) psychiatric; e) hematological/immunological, f) endocrinological, g) ophthalmic and h) renal. The assessment data shows the individual performed one or more exams within that assessment category to detect possible alterations. Psychopedagogical assessment was also available in the BDCA and analysed separately as a supportive therapy. Consequently, not being used to map the therapeutic itinerary.

The groups of clinical alterations associated with 22q11.2DS and available in BDCA were neuropsychomotor development, lip and/or palate, cardiac, psychiatric, hematologic/immunological, endocrinological, auditory, ophthalmological, genitourinary and gastrointestinal tract. Information about the presence or absence of each of these alterations was not available to all individuals. For this reason, these analyses include a different total sample for each clinical characteristic.

Statistical analysis

Frequency tables for categorical variables and measures of position and dispersion for numerical variables were used to describe the sample profile. We used Chi-square or Fisher's exact test to compare categorical variables and Mann-Whitney and Kruskal-Wallis tests to compare numerical measurements. The significance level adopted was 5%.

Results

General data of the casuistry and age at diagnosis

Of the 111 individuals, 64/111 (57.7%) were female and 47/111 (42.3%) were male. The median age of the sample group was 9 years of age (sd = 7.2, mean = 9.7 years, mode = 6). The geographical distribution shows that 6/111 (5.4%) come from the Northeast, 39/111 (35. 1%) from the Southeast and 66/111 (59.5%) from the South. The median age at diagnosis was 9 years, with the minimum value equal to 0 years and a maximum of 33 years (sd = 7.2, mean = 9.7 years, mode = 6).

Sgardioli *et al.* 2019 previously published age of diagnosis data obtained at BDCA from 2008 to 2017. For this article, we add patients seen for diagnosis from 2018 until 2020. However, the general approach of this study is unprecedented.

From years 2008 to 2014, before the establishment of Comprehensive Care Policy for People with Rare Diseases (PAIPDR - Ordinance GM/MS nº 199/2014) the median age of diagnosis was 9 (sd = 7.5, mean = 10.6, mode = 9, minimum value = 0 and maximum value = 33). After the establishment of PAIDR, from 2015 until 2020, the median age of diagnosis was 8 (sd = 6.5, mean = 8.3, mode = 11, minimum value = 0 and maximum value = 24).

Clinical changes and age of diagnosis

The 5 most recurrent clinical alterations in the total sample (N = 111) were: neuropsychomotor developmental delay 85/97 (87.6%), lip and/or palate defects 87/101 (86.1%), cardiac malformation 68/96 (70.8%), hematological/immunological alteration 57/81 (70.4%) and psychiatric disorder 49/83 (59%) (Table 1).

Table 1 *Clinical manifestations in the total sample*

	N° of individuals /Total	%
NPMDD*	85/97	87.63
Lip-palatal defect	87/101	86.14
Cardiac Malformation	68/96	70.83
Hematological/immunological alteration	57/81	70.37
Psychiatric disorder	49/83	59.04
Alteration of the gastrointestinal tract	43/79	54.43
Hearing deficiency	36/81	44.44
Ophthalmological alteration	30/71	42.25
Endocrinological alteration	13/35	37.14
Alteration of the genitourinary tract	12/60	20

*Neuropsychomotor developmental delay

Individuals with a cardiac malformation had a lower median diagnostic age when compared to individuals without cardiac malformation, corresponding to 6.5 and 11 years of age (p = 0.0006242),

respectively. Conversely, individuals with psychiatric disorder and lip and/or palate defects had a higher median diagnostic age than that found in individuals without these alterations, equivalent to 10 versus 7.5 years (p = 0.05677) and 10 versus 1.1 years (p = 0.0004966), respectively.

Concomitant clinical manifestations

Among the 85 individuals with neuropsychomotor development delay, 74 (87.1%) also presented lip and/or palate defect, 49 (57.7%) presented a cardiac malformation and 45 (52.9%) presented a hematological/immunological alteration (Fig. 1).

In the group of 87 individuals with lip and/or palate defects, 74 (85.1%) had neuropsychomotor development delay, 47 (54%) had a cardiac malformation and 44 (50.6%) had a hematological/immunological alteration (Fig. 2).

In the 68 individuals with a cardiac malformation, 49 (72.1%) presented neuropsychomotor development delay, 47 (69.1%) presented lip and/or palate defect and 33 (48.5%) presented a hematological/immunological alteration (Fig. 3).

Among the 57 individuals with a hematological/immunological alteration, 45 (79%) also presented neuropsychomotor development delay, 44 (77.2%) presented lip and/or palate defects and 33 (57.9%) presented a cardiac malformation (Fig. 4).

Access to expert assessment and age of diagnosis

Among the 12 evaluations recommended at the time of diagnosis, 8 were available in the BDCA. The average access was 5.5 (68.75%) evaluations per individual (minimum value equal to 1 and a maximum of 8, median and mode = 6).

The 3 most accessed evaluation were nasopharyngeal 107/111 (96.4%), cardiac 104/111 (93.7%), and psychiatric 83/111 (74.8%). The least accessed was endocrinological 35/111 (31.5%) (Table 2). Individuals with ophthalmological, psychiatric and nasopharyngeal assessments had a higher median age of diagnosis, equivalent to 10 versus 7 years (p = 0.004917), 10 versus 4 years (p = 0.002412) and 9 versus 0 years (p = 0.002302), respectively.

Table 2 *Health Assessments available at BDCA and performed by the total sample*

	N° of individuals /Total = 111	%
Nasopharyngeal	107	96.40
Cardiac	104	93.69
Psychiatric	83	74.77
Hearing	81	72.97
Hematological/Immunological	81	72.97
Ophthalmological	71	63.96
Renal	48	43.24
Endocrinological	35	31.53

Access to supportive therapy

Among the 111 individuals, 14 (12.6%) accessed psychopedagogical assessment.

Discussion

Although 22q11.2DS is the most frequent microdeletion in humans, its diagnosis and management are still universally challenging (3, 4, 20, 21). Considering the continental dimensions of Brazil and that the key access to health of the population is through SUS (22), it is essential to seek strategies that facilitate suspicion, investigation and management of this clinical condition. In this context, the BCFP has brought information to subsidize health actions for this population group (8, 15). The perspective of this study is to characterize the clinical trajectories of individuals registered in BDCA until their 22q11.2DS diagnosis. The difference in the percentage of cases between Brazilian regions herein presented only reflects the demand registered by the BCFP participating centers and has no epidemiological value.

The Comprehensive Care Policy for People with Rare Diseases (PAIPDR) establishes as a role of primary care the identification of clinical characteristics that may suggest the need for referral to specialized or reference services in rare diseases (10). However, individuals with important characteristics of 22q11.2DS are arriving late to the reference services, which may compromise therapeutic interventions and genetic counseling of parents.

Individuals with psychiatric disorder (49/83) had a higher median age of 22q11.2DS diagnosis (10 years with psychiatric disorder versus 7.5 years, without a psychiatric disorder). Up to 40% of individuals with intellectual disability have a psychiatric disorder (23), which can contribute to the deficient association between this phenotype and 22q11.2DS. In 22q11.2DS, these alterations manifest more frequently in adolescence (4, 5, 24), which would make the early diagnosis impossible if this was the most evident characteristic of this syndrome in an individual. Instead, in this study, over 53.1% of individuals with a psychiatric disorder also presented other important characteristics of 22q11.2DS, such as NPMDD, lip and/or palate defects, cardiac malformation and/or hematological/immunological alteration.

Similarly, individuals with lip and/or palate defects alone had a higher median age of diagnosis (10 years with lip and/or palate versus 1.1 years without lip and/or palate defects). These defects occur more frequently in isolation (25) but are present in at least 600 other Mendelian syndromes (26). Among these, 22q11.2DS is the most frequent microdeletion (27, 28). In this study, at least 50.6% of the individuals who presented lip and/or palate defects (87/101) also presented other clinical manifestations indicative of 22q11.2DS, such as NPMDD, cardiac malformation and/or hematological/immunological alteration.

The presence of a cardiac malformation was a significant variable of reduction of the diagnostic age (median of 6.5 years with a cardiac malformation versus 11 years without cardiac malformation). Other studies had similar results (20, 29). In total 70.8% (68/96) of the individuals had a cardiac malformation, which is one of the most recognized characteristics of 22q11.2DS.

These results suggest that there is difficulty of 22q11.2DS clinical suspicion or obstacles in referral and access to the genetic service. In any case, the need for improvement in the flow of primary care-

specialized/reference service is a reality. Added to this is the absence of geneticists as a requirement for the registration of hospitals that perform integrated procedures for aesthetic-functional rehabilitation of patients with lip-palate malformation by SUS (Brazilian Ordinance SAS/MS No. 62) (30).

In this study, at least 72.06% of individuals present 2 or more recurrent clinical manifestations indicative of 22q11.2DS concomitantly. They are also common abnormalities in this disorder (3). Therefore, an increase of health professional's awareness about 22q11.2DS phenotype would enable its clinical suspicion even under its phenotypic variability. In this sense, Monteiro and collaborators proposed clinical characteristics for the suspicion of 22q11.2DS and indication of laboratory investigation (15), which were later validated (8).

Using this data to produce information resources aimed at training health professionals is essential for better effectiveness and efficiency of the flow of primary care-reference service. The set of this information can also contribute to the establishment of the national protocol for clinical management of 22q11.2DS and the national standardization of care. Finally, the training of health professionals besides the establishment of the national management protocol are important tools to achieve early diagnosis of 22q11.2DS (8).

Still, within PAIDR, individuals referred to the reference services in rare diseases should return to primary and secondary care to receive multi-professional care according to the therapeutic plan established by the reference team (10). Counter-reference enables individuals to perform evaluations in health units in their region, increasing treatment adherence. In this study, individuals accessed 68.75% of the evaluations available in the BDCA and recommended at the time of 22q11.2DS diagnosis (9). These evaluations happened before the diagnosis, reinforcing the unfamiliarity with this syndrome by health professionals and (or) the difficulty to access genetic evaluation and test.

Individuals that accessed psychiatric and nasopharyngeal assessments had a higher median age of diagnosis, of 10 versus 4 years of age and 9 versus 0 years, respectively. These results add to those got in the presence of psychiatric and lip and/or palate defects versus age of diagnosis and corroborate with the perception that there is an obstacle(s) in the access to the genetics service.

Endocrinology was the least accessed specialty, mentioned by 31.5% (35/111) of the sample group. In 22q11.2DS, the most recurrent endocrinological alteration is idiopathic hypocalcemia, which may be present in up to 60% of individuals since neonatal period (5). This is a 22q11.2DS characteristic manifestation and therefore important for its clinical suspicion and referral to the medical genetics service. We should note that the number of endocrinologists working in SUS is 6990 (31), which makes universal access to this professional very restrictive.

Only 12.6% of the sample group accessed psychopedagogists. Psychopedagogical follow-up is a key aspect for recognition of individual potentials and difficulties, favoring school performance and psychosocial insertion. Psychopedagogy is among the support therapies advocated in reference centers for rare diseases and is mainly indicated in the presence of NPMDD (10). In this study, NPMDD was the

recurrent clinical alteration. The number of psychopedagogists working in SUS is 1479 (32), which makes universal access to this professional difficult.

Given the diversity and quantity of rare diseases, raising the suspicion of a specific condition is challenging, but there are possible paths to tread when faced with a complex clinical disease without a defined cause.

It is up to primary health care the recording of the medical history, which includes a meticulous clinical evaluation, active listening, recording of family history and anamnesis. The referral to specialized care allows the performance of a complete check-up, facilitating the detection of cardiac, immunological, endocrinological, neurological, genitourinary and gastrointestinal tract alterations. (10). The set of this information can narrow the range of possible rare diseases and contain possible health aggravations in individuals who have not yet accessed the reference service for rare diseases.

Before the establishment of the PAIPDR (2008–2014), of which some BCFP services are part, mean age of 22q11.2 DS diagnosis obtained was 10.6 years while after PAIPDR (2015–2020), the mean age of diagnosis was 8.3 years. Although the trend was a reduction, both averages are far from ideal.

The consequences of delayed diagnosis associated with incomplete management are many. We highlight the worsening of untreated clinical manifestations and in the prognosis of this individual, the delay in the family's preparation to deal with the evolution of the clinical condition and the increase in the costs associated with health for both the patient and the state.

In Canada, the mean age of diagnosis of 22q11.2DS is 4.7 years (20) and adult individuals with 22q11.2DS, with continuous interdisciplinary follow-up, have a life expectancy of 46.4 years (33).

Data on post-diagnosis management and life expectancy of Brazilian individuals with 22q11.2DS are not available. The absence of these data makes it impossible to optimize the PAIPDR to ensure that increased life expectancy comes with early diagnosis and increased quality of life.

The lack of 22q11.2DS data from the North and Midwest and the few cases from the Northeast prevented the comparison of the therapeutic itinerary until the moment of diagnosis between the different regions of Brazil. It is noteworthy that BCFP does not has partner centers in the North and Midwest. However, considering that socioeconomic and demographic differences between the five regions of the country correlate directly with the availability and quality of health services (34, 35), the number of evaluations accessed by individuals with 22q11.2DS from different regions may vary.

From this perspective, the small proportion of genetic services in the North (11, 36) added to the reduced number of geneticists in Brazil, allocated mostly in the Southeast (37,38), makes fair access to early diagnosis less probable.

Following the international recommendations for diagnosis, clinical management of 22q11.2DS and the characteristics of the Brazilian Unified Health System (4, 9) we suggest a flowchart with general lines of

health care (Fig. 5):

Whereas clinical management should be based on recommendations for each age group, but the establishment of the therapeutic plan should be individualized, the proposed flowchart may guide the multidisciplinary team to define the longitudinal therapeutic plan.

This was a retrospective, cross-sectional study and as one, it has restrictions of working with available data collected through the years. Furthermore, some information is collected from the report of individuals with 22q11.2 DS and/or their responsible, therefore it may contain comprehension and memory bias. Considering Brazil's inequalities regarding socioeconomic aspects and access to health care it also may contain biases associated with availability and ease of access to health services.

Conclusions

In conclusion, early suspicion and diagnosis of 22q11.2DS depend on the training of health professionals and access to diagnostic tests. From this, the structuring of clinical management according to the specific lines of care would lead to interventions in time to get the best results for each clinical situation. If this strategy is established as public health policy, the integral approach of each individual will favor its complete biopsychosocial insertion.

Abbreviations

22q11.2DS
22q11.2 Deletion Syndrome; NPMDD:delayed neuropsychomotor development, BCFP:Brazil's CranioFacial Project; BDCA:Brazilian Database on Craniofacial Anomalies; PAIPDR:Comprehensive Care Policy for People with Rare Diseases, SUS:Unified Health Care System, CMA:Chromosomal Microarray Analysis; FISH:Fluorescent in situ Hybridization; MCA:Multiple Congenital Anomalies; MLPA:Multiplex Ligation Probe-dependent Amplification; - Famerp:Faculty of Medicine of São José do Rio Preto, UFRGS:Federal University of Rio Grande do Sul, CAIF:Cleft Lip and Palate Integral Care Center, CADEFI:Center for Attention to Defects of Face, HUPAA:Professor Alberto Antunes Hospital, UFAL:Federal University of Alagoas, APAE:Association of Parents and Friends of the Exceptional from Sao Paulo, CAISM:Center for Comprehensive Women's Health Care, Unicamp:State University of Campinas

Declarations

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Authors' contributions

All authors were involved in data collection and interpretation, reviewing and approving the manuscript for submission.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

This study was approved by the Ethics Committee Board of the University of Campinas, CAAE: 2477419.1.0000.5404. All participants or their legal guardians signed the informed consent form.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author's information

Not applicable.

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Figures

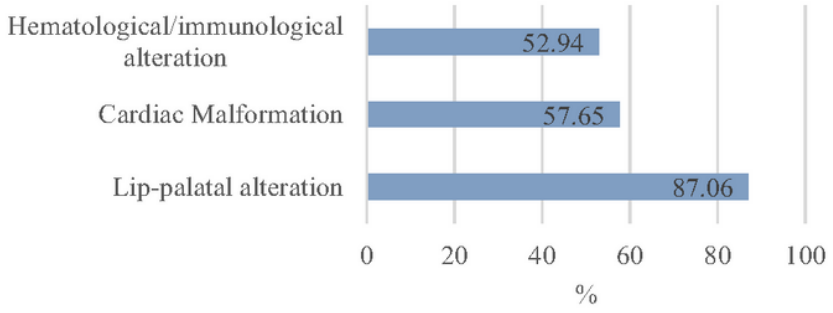


Figure 1

Recurrent clinical manifestations in the 85 individuals with delayed neuropsychomotor development.

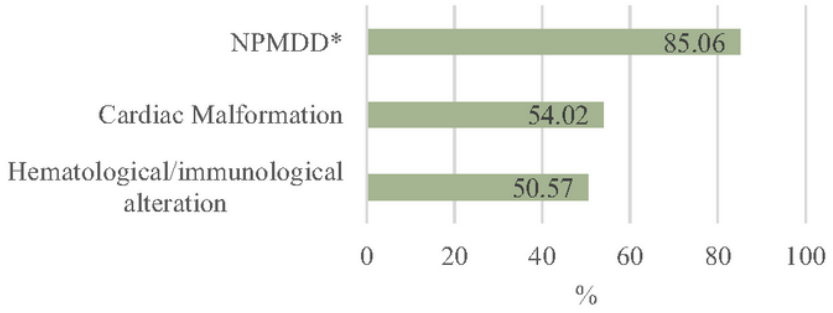


Figure 2

Recurrent clinical manifestations in the 87 individuals with alteration in the lip and/or palate. *Neuropsychomotor developmental delay

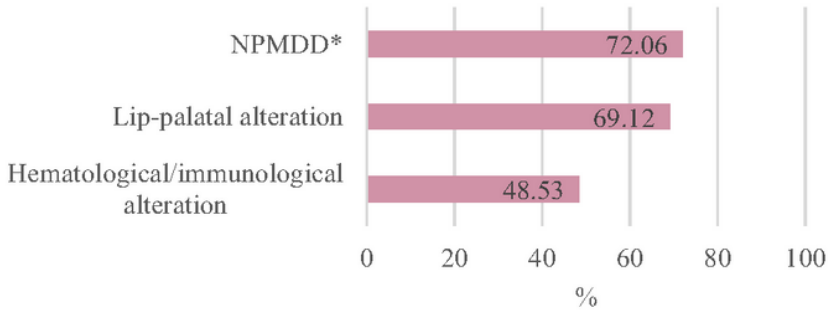


Figure 3

Recurrent clinical manifestations in 68 individuals with cardiac malformation. *Neuropsychomotor developmental delay

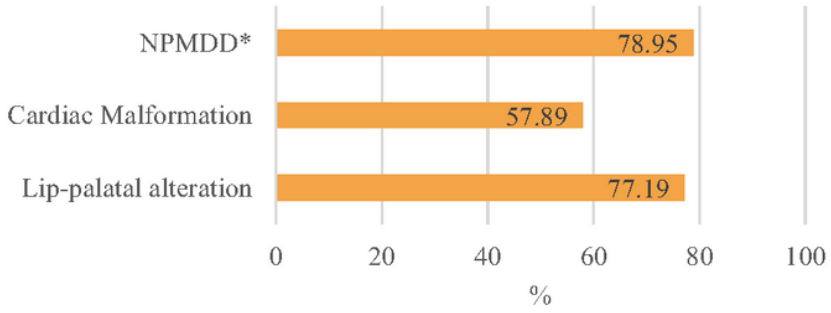
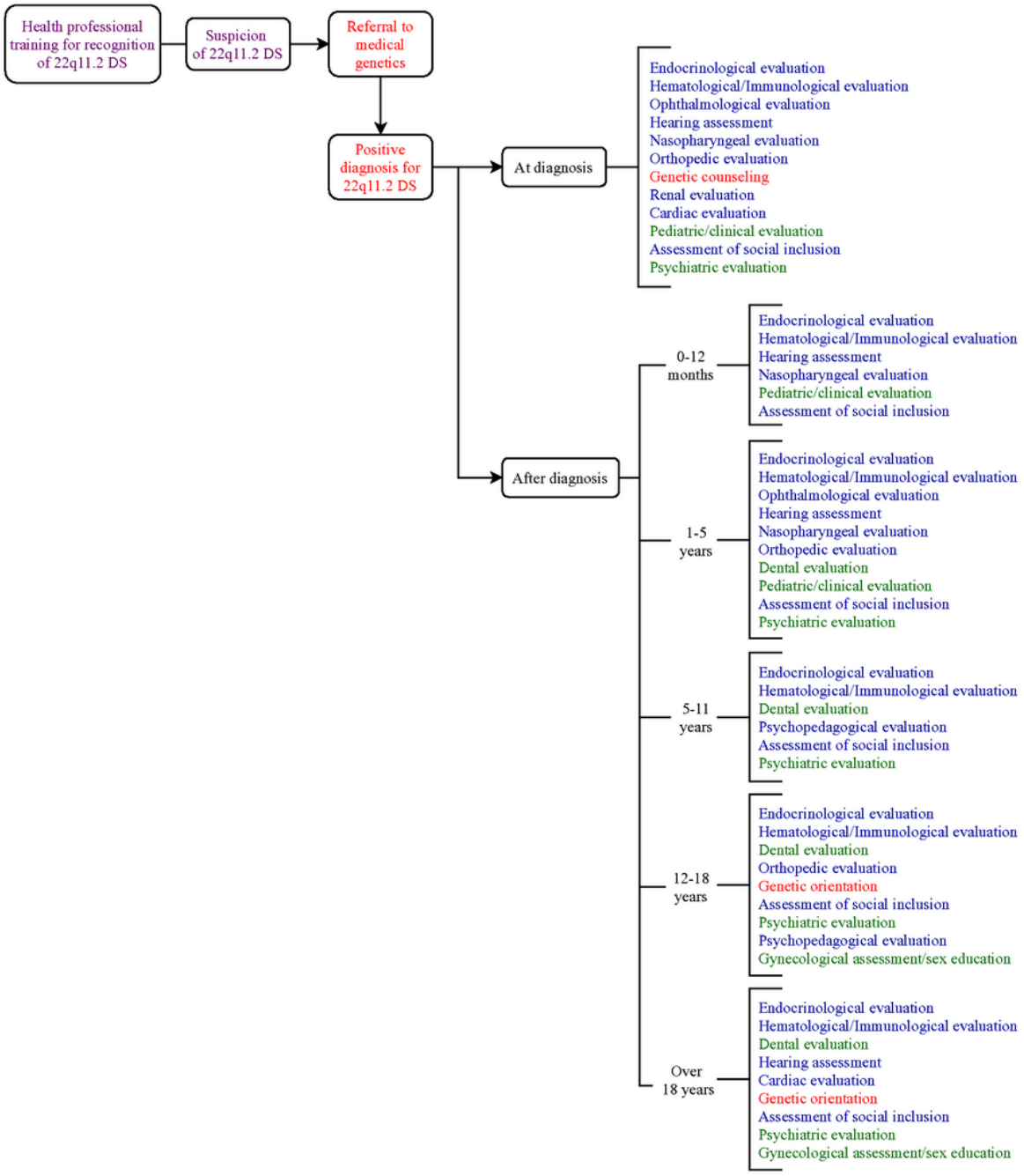


Figure 4

Recurrent clinical manifestations in 57 individuals with haematological/immunological alteration.
*Neuropsychomotor developmental delay



Obs.: Green letters refers to primary care, blue refers to secondary care, red refers to tertiary care and purple refers to primary or secondary care.

Figure 5

Flowchart for clinical management of 22q11.2DS at the Brazilian Unified Health System.