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SUMMARY

FRAGILE X SYNDROME: THE ROLE OF MOLECULAR DIAGNOSIS AND SCREENING IN AN INTEGRATED APPROACH TO SERVICES

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and
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Report submitted to the
Québec Minister Responsible for Research, Science and Technology

MISSION

To assist the Minister of Research, Science and Technology and the policymakers in Québec's health-care system, including the Ministère de la Santé et des Services sociaux, by means of health technology and intervention modality assessments, specifically, by assessing their efficacy, safety, costs and cost-effectiveness, and their ethical, social and economic implications.

To assist the Minister of Research, Science and Technology in developing and implementing scientific policy.

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FRAGILE X SYNDROME: THE ROLE OF MOLECULAR DIAGNOSIS AND SCREENING IN AN INTEGRATED APPROACH TO SERVICES

In 1996, the *Conseil d'évaluation des technologies de la santé (CETS)* started a project on the problems posed by the transfer of knowledge from medical genetics research to new clinical applications. The *Agence d'évaluation des technologies et des modes d'intervention en santé*, as *CETS* was renamed, with the support of a multidisciplinary committee, is thus examining technologies derived from molecular biology, which is making available an increased number of diagnostic and prenatal tests for many diseases.

CETS chose four diseases as a priority, namely, Duchenne and Becker muscular dystrophies, myotonic dystrophy, tyrosinemia and fragile X syndrome, its criteria being the seriousness and incidence of the disease, test availability and reliability, and the availability of preventive measures. The fourth and present report in this series concerns fragile X syndrome, the leading cause of mental retardation, after Down's syndrome. Its prevalence is at least 1 per 4,000 males and 1 per 8,000 females. Early clinical diagnosis of this disease is difficult.

This assessment summarizes the state of knowledge regarding the genotypic analysis of individuals with the syndrome and screening for asymptomatic carriers of a dynamic mutation on the FMR1 (fragile X mental retardation 1) gene. This report also discusses the usefulness of developing or maintaining such a service in Québec's health-care system and the management of affected individuals by medical, social and educational services, and explores the ethical issues involved.

In conclusion, the *Agency* believes that the conditions are in place for one or two laboratories meeting the necessary standards of quality to perform diagnostic tests for fragile X syndrome. Other implications regarding the clinical support and follow-up to be provided to the families concerned, the necessary medical, social and educational resources, research, and the organizational aspects of the services are discussed as well.

With this assessment, the *Agency* wishes to provide the best possible information to the policymakers in the many sectors concerned with this problem and its impact on affected individuals and families.

Renaldo N. Battista
President and Chief Executive Officer

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Introduction

In 1996, the *Conseil d'évaluation des technologies de la santé (CETS)* started a project on the problems posed by the transfer of knowledge from medical genetics research to new clinical applications. The *Agence d'évaluation des technologies et des modes intervention en santé*, as CETS was renamed on June 28, 2000, with the support of a multidisciplinary committee, is examining technologies derived from molecular biology, which is making available an increased number of diagnostic and prenatal tests for many diseases.

CETS chose four diseases as a priority, namely, Duchenne and Becker muscular dystrophies, myotonic dystrophy, tyrosinemia and fragile X syndrome, its criteria being the seriousness and incidence of the disease, test availability and reliability, and the existence of preventive measures. Reports have already been published on the first three diseases. The present assessment therefore concludes this series on monogenic diseases.

In general, this report examines the state of knowledge regarding the genotypic analysis of fragile X individuals and healthy carrier screening, and explores the usefulness of developing such a service in our health-care system. Specifically, it first describes the disease, its management and its genetic aspects. It then investigates the impact on genetic counselling, examines the diagnostic indications and describes the molecular diagnostic protocols. Test performance, diagnostic strategies and especially strategies for screening for healthy carriers in the family and for screening pregnant women or women of child-bearing potential are discussed as well. Then, after describing the situation in Québec, the assessment devotes special attention to the

many social and ethical issues surrounding the identification of the syndrome, to the professional interventions and to the different aspects of planning and organizing services. The report concludes by proposing specific approaches for adequately meeting the needs of affected individuals and families.

Overview of the syndrome

Fragile X syndrome is the second leading cause of mental retardation, after Down's syndrome. Fragile X syndrome is identified in about 2% of boys with mental retardation and in more than one third of families with a history of X-linked mental retardation. The prevalence is at least 1 in 4,000 males and 1 in 8,000 females.

This X-linked, dominant, monogenic disease exhibits an unusual mode of transmission, affecting both sexes, but with variable penetrance and expressivity. Most affected boys present with moderate to severe mental retardation, while only 55% of affected girls will have mental retardation, generally mild to moderate. Cognitive impairment can manifest as delayed language acquisition and developmental delay well before mental retardation is considered. The most typical physical signs (facial dysmorphism, macroorchidism) usually appear during adolescence, with behavioural problems, such as hyperactivity and attention disorders, appearing mainly during childhood and adolescence. The clinical picture therefore varies enormously, and no sign is pathognomonic. As a result, early clinical diagnosis is difficult, especially if there is no known family history of the syndrome.

While most of the needs generally result from mental retardation, language acquisition problems, learning disabilities, and behavioural and socialization problems create additional needs,

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which must be factored into the offer of services. The management of affected individuals requires regular medical follow-up, early intervention by functional reeducation professionals (speech therapists, occupational therapists, etc.), student services throughout the patient's schooling, and social integration and adaptation services. A concerted, multidisciplinary approach based on a needs assessment and individualized planning of services is best for optimizing the potential for these children's development and for promoting their autonomy and social integration. Additionally, the family requires information and support and should receive genetic counselling as soon as the diagnosis is made.

The contribution of genetics

In about 98% of cases, fragile X syndrome is linked to a "dynamic" mutation in the FMR1 (fragile X mental retardation 1) gene. The mutation is characterized by an expansion of variable size of a DNA sequence located in the gene's first exon and consisting of a variable number of CGG trinucleotide repeats. The alleles of the FMR1 gene are classified according to the number of repeats and the gene's methylation status. A normal allele contains between 6 and 54 triplets and is unmethylated; a premutation can contain between 55 and 200 triplets but is unmethylated; and a full mutation contains over 200 triplets and is methylated. The premutations and full mutations are unstable, their number of triplets usually increasing during mother-child transmission.

Methylation of the gene, which characterizes full mutations, seems to be what determines phenotypic expression, since it prevents the production of FMRP (fragile X mental retardation protein). Individuals who exhibit clinical signs of the syndrome therefore usually have a full mutation (or sometimes mosaics, allelic or methylation, with reduced FMRP production), whereas those who have a premutation are said to be asymptomatic

carriers and are at risk for transmitting the syndrome to their offspring. The distinction between premutations and full mutations and the dynamic nature of the mutations explain why there are males and females who are obligate carriers but who are asymptomatic, the occurrence of the disease in families with no family history of mental retardation, and the increased penetrance in subsequent generations (the phenomenon of anticipation).

Molecular analysis of the FMR1 gene, which has been available as a clinical service since 1992, constitutes a substantial gain over the earlier cytogenetic analyses, which were prone to classification errors and unreliable in females. Molecular testing clearly establishes the diagnosis in symptomatic individuals, identifies individuals at risk for transmitting the syndrome and, by identifying the type of mutation, provides a more accurate estimate of the risk of transmitting the syndrome.

Developments in molecular genetics are thus an important contribution to genetic counselling, since they are making it possible to determine the genotypic status of an affected individual's relatives more accurately, reassuring some and permitting the others to make their reproductive decisions on the basis of a more accurate determination of the risks of transmitting the syndrome. However, certain limits in the current knowledge of genotype-phenotype correlations and of the meiotic stability of the alleles have an impact on genetic counselling and reproductive choices. The main problem concerns the decision facing couples when a prenatal diagnosis reveals a full mutation in a female fetus, since, in such cases, it is impossible to state with certainty if and to what extent there will be any intellectual impairment. All of these uncertainties and the resulting problems should be clearly explained to couples during genetic counselling so that they can base their decisions on sound, complete and up-to-date information.

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Developmental delay and mental retardation of unknown etiology are formal diagnostic indications for fragile X testing, but they also warrant a broader workup with karyotyping, a genetic and neurological workup, and an assessment of the patient's cognitive and adaptive skills. Broadening the indications to language delay, attention disorders, autistic tendencies or learning disabilities in the absence of mental retardation would permit earlier diagnosis (so that the families could avail themselves of the necessary services sooner) and identification of a larger proportion of affected individuals (so that more families could obtain genetic counselling). However, relatively few studies are convincingly in support of systematically testing children with these isolated (i.e., in the absence of mental retardation) clinical signs. While the usefulness of the diagnostic test for these indications can be examined on a case-by-case basis in a clinical practice setting, the use of proactive diagnostic and carrier screening strategies founded on broadened indications should be based on more research and a more thorough assessment. Lastly, it now seems justified to screen for a premutation in prematurely menopausal women.

Genotypic analysis for fragile X syndrome entails the use of two techniques—Southern blot and PCR, which are performed sequentially. The reference method for diagnostic tests consists of the Southern method with double enzyme digestion, a modified method for identifying large expansions and determining the gene's methylation status, followed, if need be, by PCR in order to accurately determine the size of the normal and premutated alleles. This protocol permits genotypic diagnosis for most of the families concerned, since point mutations and deletions apparently account for at most 2% of the mutations associated with the syndrome. A number of researchers recommend protocols in which PCR is performed first, with selective confirmation by Southern blot. Such an approach would have the

advantage of being faster and less expensive, feasible with specimens other than blood (e.g., a buccal smear) and better suited to large-scale screening. However, neither of these methods has been compared, in a rigorous and systematic fashion, with what is considered the reference method. Lastly, immunocytochemical analyses of FMRP expression are still in the research stage.

Instituting quality controls would be desirable, given the possible performance variability due to experimental conditions. Furthermore, the expertise required to interpret the results underscores the importance of close collaboration between research laboratories and clinical laboratories. Lastly, with regard to prenatal diagnosis, it is advisable to use both methods, Southern blot and PCR, routinely. Also, couples should be told that prenatal diagnosis, especially when performed by chorionic biopsy, can sometimes be inconclusive.

Situation in Quebec

Since no research project or program for identifying symptomatic individuals has been set up in Québec, it is difficult to accurately determine the number of affected people, especially since there is no register, association or specialized centre that can provide such data. According to a theoretical calculation based on the latest prevalence estimates, there were, in Québec in 2000, 250 affected children under the age of 15 years, for a total of 1,377 affected individuals. Upon comparing this figure with the approximate number of people in whom a diagnosis was made, it is seen that the syndrome is underdiagnosed, both in Québec and elsewhere. At the same time, a major study revealed that the prevalence of the premutation is 1 in 259 females in Québec.

Molecular tests for the FMR1 gene are performed by two laboratories. They have been available at the laboratory of CHUQ's Depart-

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ment of Biochemistry (Saint-François d'Assise Branch) since late 1991, and Hôpital Sainte-Justine's molecular biology laboratory developed a test in 1997. The reference method is currently used at the Saint-François d'Assise Branch, whereas at Hôpital Sainte-Justine's molecular biology laboratory, an alternative method in which PCR is performed first and whose analytical validation has yet to be documented in the literature, was used initially. However, in light of the preliminary results of a recent validation project carried out jointly with CHUQ's laboratory, those in charge of Hôpital Sainte-Justine's laboratory plan to modify their diagnostic protocol.

The number of test requests is gradually increasing, having been 700 to 800 annually for the past few years. It seems that an increasing number of requests are being made because of developmental delay and learning disabilities and that there is a trend toward earlier diagnosis. Given this trend toward using broader indications and the facts that the syndrome is underdiagnosed and that some families have not yet been identified, the demand is likely to remain stable or continue to grow in the next few years. The funds allocated for interhospital billing for genetic tests are one of the factors that could limit the demand for the tests and compromise equal access to them. Lastly, although the above-mentioned laboratories are currently able to meet the demand, their capacity should be reassessed in the event of a substantial increase in demand, which could happen if there is a practice change or if pilot projects are set up for the purpose of evaluating new diagnostic and screening strategies.

While it may be justified at this time to have, in Québec, two laboratories for performing these tests, considering the increasing demand for testing and the ordering recommendations issued by professional organizations, it would not be beneficial to increase the number of laboratories offering tests, given the expertise required to perform and interpret it and the importance of close

collaboration between research laboratories and clinical laboratories. Furthermore, it would be beneficial for the diagnostic protocols to be harmonized and for a quality control system to be instituted for all molecular tests.

Upon examining the situation in Québec, it is seen that there is presently no specific medicosocial or educational management of affected individuals or families. With the movement to deinstitutionalize the mentally impaired and integrate them into schools and society, this management is provided both or alternatively by the medical community, CLSCs, schools and rehabilitation centres in conjunction with the family. Because of the involvement of all these sectors, with their respective responsibilities, and the progressive and multifaceted nature of fragile X syndrome, there are: 1) numerous points of entry and channels leading to a diagnosis; 2) nonstandardized approaches to the diagnostic workup; 3) different management modalities for reeducation and social integration; and 4) several types of educational paths.

This diversity of individual paths does not, as such, pose a problem as long as service accessibility, continuity and complementarity are ensured. These conditions can be fully realized only if the necessary services are available and effectively coordinated. Despite the efforts made in the health and social services system to improve organizational coordination and despite the options available through the development of individualized service plans for promoting service continuity and complementarity at the individual level, we must recognize that the obstacles to coordination contribute to hindering access to services and that optimal use of the resources is undermined because they are scattered. Furthermore, the availability of certain services has been reduced because of budget cuts over the last few years and the shortage of certain human resources in the health and social services and educational systems. Lastly, all of

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these problems are exacerbated by a lack of communication and collaboration between the medical, social and educational sectors.

The service accessibility, continuity and complementarity problems place an additional burden on affected individuals and their families. The parents, who already have to look after special-needs children on a daily basis, are often forced to undertake demanding administrative tasks and negotiate, in order to obtain services, with the various sectors responsible for them. As for affected children, the lack of timely services and the continuity problems, which disrupt the stability of their environment, could have a negative impact on their development.

Given the current deficiencies in the provision of services and given the responsibility of the promoters of a diagnostic and screening strategy, the usefulness of early diagnosis (for case-finding strategies) would hinge on improving, over the present situation, the accessibility, continuity and complementarity of the services provided to the families concerned. In this regard, it is seen that benefits could be achieved as long as a substantial effort to inform professionals enables them to use the diagnosis as a service planning and coordination tool.

While there may not be any recognized direct therapeutic benefit for affected individuals, early diagnosis would unquestionably be beneficial in terms of defining their needs and those of their families. Confirming the diagnosis in a symptomatic individual could thus contribute to better planning of the necessary care and services. Even if this contribution is difficult to assess, it would be of the utmost importance to design the offer of testing in tandem with better coordination of efforts to improve the referral of affected individuals and their families to the available services, to improve timely access to the necessary services and to adapt the available services

to the specific needs of affected individuals and their families.

Diagnostic and Screening Strategies

Depending on whether one diagnoses and screens for affected individuals (current clinical diagnostic practice; prenatal diagnosis; diagnosis and proactive screening in high-risk populations; neonatal screening) or screens for carriers at risk for transmitting the syndrome (cascade screening, screening of women with a history of mental retardation or other signs; screening of pregnant women with no particular family history; preconceptional screening of women of child-bearing potential), the objectives are not the same. With regard to diagnosing and screening for affected individuals, the impact usually anticipated when making an accurate diagnosis is appropriate medical, psychosocial and educational management of the affected individual. As for carrier screening, its purpose is to identify individuals at risk for transmitting the syndrome to their offspring and, through genetic counselling, to enable them to make informed reproductive choices. Usually, cascade screening is performed after an individual is diagnosed with the syndrome.

To evaluate screening strategies, one assesses the utility, feasibility and acceptability of the various proposable strategies. To do this, accumulated international experience should be applied to the local context, which partly determines their feasibility and acceptability, as well as their utility. In this regard, too often we have to rely on incomplete data concerning the utility and acceptability of strategies for which international experience is limited.

A number of arguments can be presented to demonstrate the usefulness of screening low-risk populations. The syndrome is underdiagnosed; about one third of cases of the syndrome occur in families with no family history of mental retardation; the prevalence of premutations is

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dation; the prevalence of premutations is high; and the proportion of carriers that can be identified by screening high-risk individuals followed by cascade screening would be significantly lower than the results anticipated for more systematic screening of low-risk populations. However, neonatal screening cannot be recommended at this time because of the problems involved in identifying premutation carriers and because early management does not confer any benefit. Also, preconceptional screening and the systematic screening of pregnant women with no particular family history are subject to the limits of our prognostic capabilities. These weaknesses basically concern the risk of a maternal premutation expanding into a full mutation in her children where there is no family history and predicting cognitive impairment in female fetuses carrying a full mutation, two essential elements for determining the risk of transmitting the syndrome to the offspring. Since screening low-risk women is recognized as potentially having some usefulness, despite what little experience has accumulated at the international level, it is to be hoped that the pilot projects currently underway in various countries are adequately examining the benefits, risks and main issues that determine the acceptability of these approaches.

As for proactive high-risk-population screening strategies, there is vast international experience suggesting that the existing programs are generally well accepted and that they meet a need on the part of families, if followed by cascade screening. However, this approach has certain limitations that are now clearly known: these programs end up achieving a decreasing case-finding yield; the screening of the families is often incomplete; and carriers with no family history cannot avail themselves of this service. Furthermore, most studies have concerned themselves with a limited number of indications, mainly mental retardation, and therefore do not address the additional objective—now a given—of identifying affected individuals as

early as possible. Achieving this objective would require a broadening of the diagnostic indications and the concurrent use of other selection criteria, two facets of screening on which there is precisely no consensus in the literature. Also, the feasibility of this strategy clearly depends on the regional organization of services and especially on the centralization of the educational and specialized services provided to the clientele of interest. Yet, it seems that, in Québec, given the extent of the movement toward social and school integration, the management of developmentally delayed, mentally retarded and learning-disabled children varies enormously and is very decentralized, both from a medical, social and educational standpoint. Lastly, a selective, proactive approach in Québec has not yet achieved social acceptability because the population and many health professionals are ill-informed about the syndrome.

Consequently, no proactive high-risk-population screening strategy or no low-risk-population screening strategy can be recommended at this time due to the facts that such strategies raise numerous ethical issues which need to be debated and that a number of scientific problems first need to be resolved. Furthermore, there would need to be validated tests suited for wide-scale screening. The methods and knowledge in this area are evolving at an extremely rapid pace, with the result that, in the future, the situation will have to be reassessed in light of the new developments.

For the time being, we will therefore have to rely more heavily on an improvement in the current practice of diagnosing affected individuals (clinical practice meeting the demand of families of symptomatic individuals) and of screening for people at risk for transmitting the syndrome to their offspring (cascade screening and prenatal diagnosis if there is a family history of the syndrome; screening of pregnant women with a family history of mental retardation if the diagnosis

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cannot be made beforehand in a symptomatic relative). In this regard, the deficiencies found upon examining the situation in Québec are of several types. The variability and insidious occurrence of the symptoms and the relative lack of knowledge of this clinical entity by first-line health professionals, the numerous points of entry into the system, the lack of collaboration between the health-care system and the school and preschool system, and the absence of a standardized workup for developmental delay and mental retardation lead to highly variable recruitment channels and unplanned prescreening and result in the fragile X syndrome remaining underdiagnosed. In addition, the "prediagnostic" path is described by parents as being difficult and painful, and the psychosocial support system after the diagnosis is communicated, timely access to genetic counselling, and referrals to the necessary support and integration services vary enormously. Lastly, the mode of service organization not only has an impact on the recruitment channels leading to a diagnosis, but also on the management of affected individuals and their families.

Improvement to the current practice could therefore be considered at several levels: that of professional practice and that of the organization of services, together with broader dissemination of information. From the standpoint of professional practices, the development and dissemination of a standardized workup for developmental delay and mental retardation would have the advantage of promoting greater diagnostic accuracy, which would be of benefit to all the children concerned. From an organizational standpoint, the problem of intersectorial coordination is the most obvious one. Any effort to make improvements should essentially be aimed at promoting the integration of the diagnostic and medical follow-up services, the cognitive and functional assessment, and the offer of reeducation and integration services. Such an objective could, for example, be achieved either by setting up a referral network

or by creating truly multidisciplinary centres dedicated to mental retardation, but also to precursor signs, such as developmental delay or language acquisition delay. Any steps in this direction will mean greater responsibility on the part of the professionals and organizations involved and substantial cooperation.

Ethical and Social Aspects

Fragile X syndrome diagnosis and screening in affected families, the situations in which the tests are ordered, and the organization of the services relating thereto have certain ethical and social implications.

In the identification of fragile X syndrome, the actual diagnostic workup, the communicating of the results, and the follow-up that is subsequently proposed raise certain ethical issues. The impact of a diagnosis of fragile X syndrome varies according to the setting and the situation in which the test is ordered and according to the individual or individuals concerned. The impact of identifying the syndrome, providing information to the families, the use of prenatal diagnosis, attitudes toward aborting an affected fetus and attitudes toward screening and communicating the fact that a child is a carrier are discussed in this report. The problems of stigmatization and discrimination, which are most often brought up in the context of using genetic diagnosis for non-medical purposes, can occur more acutely in the context of screening programs, like those carried out elsewhere in schools for fragile X syndrome. The sources of stigmatization are numerous. They can be the school, the community or those in charge of screening.

The quality of fragile X syndrome diagnostic and screening services depends on the test's efficacy, on the quality of the laboratory services and on the provision of clinical services, which require a sufficient number of competent personnel. A genetic test should be performed within the con-

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text of a medical procedure, with the practice standards and the protection that this context provides. For it to be judiciously incorporated into medical practice, the offer of testing should be accompanied by genetic counselling adapted to the particular characteristics of the syndrome so that complete and adequate information is provided and in order to give the psychosocial support required when providing this information. Respect for autonomy, privacy and confidentiality, ethical principles that underlie the standards of medical practice, receive an interpretation specific to the context of genetics. These practice standards, which medical genetics has adopted, should be in effect when other medical specialties are involved in the use of the tests and in providing genetic information, as is often the case for fragile X syndrome. Additionally, the possibility of commercializing the tests raises several questions relating to the assessment of their value, their interpretation, quality control and the concurrent provision of appropriate medical follow-up and genetic counselling.

Instituting a diagnostic and screening service is also a concern of the public authorities. From the standpoint of health care, the public authorities' responsibility extends to the offer of services considered necessary, the allocation of resources to different services, the organization of clinical and laboratory services, and quality assurance. As for fragile X syndrome, the numerous organizations and people involved in the offer of services, the lack of collaboration between the health-care system and the educational system, the lack of availability for ensuring efficient coordination of the services, and the numerous cuts to specialized services are forcing parents to spend time and money to obtain access to services. In short, the current context of sharing responsibilities with regard to organizing services has major repercussions on the recruitment channels leading to the demand for diagnostic tests and on the accessibility to these services by individuals with the syndrome and their families.

The social and ethical aspects of identifying fragile X syndrome underscore the need for clear guidelines for the diagnostic and screening services, this to ensure their potential benefits and minimize the prejudice that can accompany the institution of such services. Genetic professionals, who have made a significant contribution to the emergence of the current standards in medical genetics, and the health and social services professionals involved in the diagnostic workup and in providing functional reeducation and social integration services, who are in direct contact with the families, have a responsibility in this regard. Secondly, the legislature and the public authorities should put in place the necessary conditions for guaranteeing the quality and accessibility of the services offered and protect the individuals from any prejudice. It goes without saying that these services should be dispensed in accordance with the basic ethical principles of respect for a person's dignity, autonomy and privacy, and with the values that are part of the health-care system, such as fairness.

Conclusion

Consequently, the Agency believes that:

1. The necessary medical, social and educational resources should be available to meet the needs of affected families in a timely and appropriate fashion.
2. The different players in the health and social services and educational systems should examine the possible ways of improving early identification and the diagnostic workup of children with signs consistent with fragile X syndrome, devoting special attention to the services available for developmentally delayed children.

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3. One or two laboratories should be available to perform, for all of Québec, the molecular tests for fragile X syndrome in the following situations:
 - The molecular diagnosis of fragile X syndrome in a symptomatic individual with either an indication recognized in the medical association guidelines or signs consistent or associated with the syndrome, in the opinion of the ordering physician.
 - Cascade screening of an affected individual's relatives.
 - Confirmation of carrier status in a pregnant woman with a family history of signs associated with the syndrome.
 - Prenatal diagnosis, if the mother is a carrier of a premutation or a full mutation.
4. All laboratory services should be subjected to quality control.
5. The different players in the health and social services system, the educational system and the job sector should improve intersectorial collaboration at the regional level in order to improve the coordination and continuity of the services available to affected individuals and their families.
6. The issues of the accessibility, continuity and complementarity of services for fragile X syndrome reflect, in part, an organizational problem that also affects children with developmental delays of other etiologies and their families, with the result that the required efforts should be part of a coherent approach that will benefit all these families.
7. The public authorities should give preference to a mode of service organization that promotes the respect of individuals, ensures equal access to services in all regions and prevents discrimination, especially in the area of insurance.
8. Research should continue, here and elsewhere, to better document the following:
 - The epidemiology of the syndrome in the general population.
 - The risk of hereditary transmission of the syndrome.
 - Phenotype prediction.
 - The development of genetic tests better suited to wide-scale use.
 - The psychosocial impact of diagnosing, screening and genetic counselling.
9. It would be essential to evaluate, by means of pilot projects, any high- or low-risk-population diagnostic and screening strategy whose implementation is being considered, on the basis of the following criteria:
 - Its technical, organizational and economic feasibility.
 - Its efficacy in terms of the number of individuals or couples who have received genetic counselling and follow-up that meet their needs.
 - Its usefulness in terms of the services that are already available.
 - Its ethical and social acceptability.

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