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Non-invasive prenatal diagnosis of genetic diseases: a painful 'delivery' of innovative obstetrical care

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Abstract *The screening of pregnancies at risk for Down syndrome is currently based on two steps (serum markers + ultrasound examination) and is proposed to all women in France. Women considered 'at risk' are offered invasive diagnostics (amniocentesis and chorionic-villous sampling) that produce a 1–2% miscarriage rate. Thus, out of 850,000 births, 500 to 700 fetuses, mostly unaffected, are lost every year. Since 2003 the CIANE coalition has been supporting research work aimed at reducing the rate of invasive tests or development and implementation of non-invasive methods. An innovative process (ISET) able to enrich from maternal blood the very rare circulating fetal trophoblastic cells has been successfully developed by the U807 team of INSERM directed by Prof. Patrizia Paterlini-Bréchot. The ISET test has already been (phase-III) clinically validated for the prenatal diagnosis of spinal muscular atrophy (SMA) and for cystic fibrosis, but its distribution to parents of risk groups has been impeded. The protocol for clinical validation of the same test applied to non-invasive prenatal diagnosis of Down syndrome had been funded in 2006 by the French national research agency (ANR), but it was then stopped by the industrial partner of the protocol, Metagenex. Today CIANE is trying its best to bring this affair into a public debate so that the clinical validation of the non-invasive prenatal diagnosis of Down syndrome may be successfully resumed, and clinically-validated tests be put at the disposal of parents in replacement of invasive methods.*

One of the most important challenges of biomedical research, with stakes in both health and economics, is the possibility to offer pregnant women a prenatal diagnosis of genetic diseases without any risk of loosing a healthy fetus by iatrogenic miscarriage. Research is aimed at reducing the number, or reliably replacing, amniocenteses and chorionic-villous sampling, the painful and invasive current diagnostic methods that produce a 1–2% miscarriage rate. Today, in France, 500 to 700 fetuses, mostly unaffected, are lost every year (out of 850,000 births), which

constitutes a very high human cost of invasive procedures.

Since 2003, CIANE (a French coalition of childbirth associations) has been supporting research on non-invasive (or less invasive) prenatal diagnosis of genetic diseases and chromosomal abnormalities such as spinal muscular atrophy (SMA), cystic fibrosis and Down syndrome. This support is consistent with its commitment to provide informed free choice to parents and minimize risks of fetal damage. The Coalition does not endorse any moral judgment on the decision to stop or continue a pregnancy, nor does it target the implementation of systematic prenatal diagnosis. It stands up both for the right of parents to accept an affected child and for the duty of medical caregivers to put at their disposal innovative and non-invasive prenatal tests.

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From simple resistance...

In 2001–2002, a French team directed by Prof. Yves Ville conducted a successful study on the screening of pregnancies at risk of Down syndrome. The method under investigation was based on a first-trimester combined test followed by routine second trimester ultrasound examination and/or screening by maternal serum markers. The study found that this strategy would reduce the rate of amniocenteses from the 11% national average to less than 5%.

For obscure reasons, this significant advance by Ville and colleagues was not welcomed by health authorities in France. CIANE fought a battle with several institutions that were raising objections to the implementation of this new approach in the perinatal care system. Its delegates even heard officials claiming that the methodology used by the team was ‘unscientific’, a rumour that persisted until their paper was published by the American Journal of Obstetrics and Gynecology.(1)

In 2006 CIANE filed an application to the High authority on Health (HAS, *Haute autorité de santé*) which was backed by the General direction of Health (DGS, *Direction générale de la santé*) and the French national college of obstetricians and gynecologists (CNGOF, *Collège national des gynécologues et obstétriciens français*) to appoint a study group for the drafting of recommendations for prenatal screening of pregnancies at risk of Down syndrome. This action was successful as the new recommendations were published in 2007.(2)

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... to a politico-economical scandal

In 2003 CIANE became aware of research work aimed at developing and validating a non-invasive method for prenatal diagnosis of genetic diseases just requiring a blood sample collection from the future mother at the 10th week of gestation. This method, invented by Prof. Patrizia Paterlini-Bréchot from the University Paris V Descartes (INSERM, *Institut national de la santé et de la recherche médicale* Unit 807), is based on an innovative cell isolation process (ISET, *Isolation by Size of Epithelial Tumor/Trophoblastic cells*) able to enrich from maternal blood the very rare

circulating fetal (trophoblastic) cells. Cells are then invidually microdissected using a laser microscope, their genome is genotyped (versus paternal and maternal DNA) to assess their fetal origin and then used for genetic diagnosis of genomic and chromosomal abnormalities. The ISET method was clinically (phase III-)validated for non invasive prenatal diagnosis of spinal muscular atrophy (SMA) at the end of 2007 and for cystic fibrosis in early 2009.(3) The ISET process is also used to isolate rare circulating tumour cells constituting a new promising test to predict tumor recurrence, metastases or therapeutic failure and possibly, in the future, to develop an early screening of invasive cancers.(4)

In 2006, the ISET test for non invasive prenatal diagnosis of Down syndrome had been technically validated and awaited funding allowing its clinical validation. This project was submitted in March by INSERM Unit 807 to the French national research agency (ANR, *Agence nationale de la recherche*). It involved a public/private partnership with Metagenex, a company founded by Prof. Paterlini-Bréchot and her husband Prof. Christian Bréchot who sold his shares in 2001 as he had been nominated the Director of INSERM. The project was granted a 600,000 Euro funding in September 2006. Meanwhile, Metagenex had been recapitalized in July, mainly by two new investors (Axa Private Equity and Banexi Ventures Partners) who agreed to appoint Mr David Znaty as a new manager. An expert in electronics, yet inexperienced in the field of biomedical research, Znaty is the President of the powerful *Compagnie des experts agréés par la Cour de cassation*.(5)

At the end of 2006, a conflict arose when Mrs Paterlini-Bréchot became aware that Mr Znaty had not yet signed the contract with ANR, thereby preventing the public/private partners from receiving the funds. Furthermore, she had learned that, instead of activating clinical validation studies of the ISET cancer test, Metagenex was commercializing the non validated ISET test for cancer screening and cancer follow up in collaboration with the private laboratory Lavergne in Paris. Documents from Lavergne indicate that the ISET cancer test was performed without controls and without any specific training, leading to false diagnosis of cancer subsequently reported by mass media.(6)

Since her protest to the company board and manager remained unanswered, Prof. Paterlini-Bréchot questioned the two national ethical committees and the Director of the National institute of cancer (INCA, *Institut national du cancer*). Astonishingly, despite their answers asserting the need to perform clinical validation studies before marketing, Metagenex continued the commercialization of ISET as a test for cancer screening, in collaboration with Lavergne.

In this setting, INSERM and the other public institutions co-owning the four ISET patents (AP-HP and Paris V University) tried to stop the cancer test commercialization by requiring a commitment from Metagenex to market only clinically validated ISET tests prior to transferring the two remaining ISET licences.(7) Znaty and the investors refused to engage in this commitment claiming their right to obtain the licences since *"they had put the money in the company"*.(8) The manager, who was still refusing to sign the contract with ANR, informed CIANE that his position was due to the fact that the company had not received the two ISET licences.(9) Thus, despite a fierce international competition in both cancer and prenatal diagnosis

domains, the manager, backed by the company's board and investors, supported marketing of the non-validated cancer test and hampered the clinical validation of the Down syndrome test.

In June 2007 the company's board and the manager wrote to the Ministers of Health and Research (the two tutoring Ministers of INSERM) accusing the INSERM Director, Prof. Christian Bréchot, of conflict of interest. They alledged that *"Mrs Patrizia Paterlini-Bréchot, a Metagenex shareholder and the spouse of Mr Christian Bréchot, is trying by all means to slow down or impede the development of the company in order to buy its shares at a giveaway price and get back her control over it"*.(10) Actually, written documents prove that Bréchot's spouse was trying to sell shares rather than buy them.(11) However, the two Ministers commissioned two experts by the General inspection of social affairs (IGAS, *Inspection générale des affaires sociales*) to investigate the relationship between Metagenex and INSERM and public health issues related to ISET test marketing. In July 2007, the company's board and the manager filed a lawsuit against Mr and Mrs Bréchot for damage to the company asking for 42 million Euros as 'reimbursement'. They also filed a penal lawsuit against Mrs Bréchot and sued the public Institutions claiming their *"right to own the four ISET patents"*.

The IGAS report was delivered to Prof. Bréchot and his wife in September 2007. Surprisingly it did not investigate public health issues, i.e. the fact that the cancer test was commercialized despite its non-validation. Thus, since the medical-ethical reasons for being cautious about handing over the licence to Metagenex were not mentioned, the Inspectors concluded that *"there is no reason justifying the position of the INSERM Director"*. They declared that, while the honesty of the INSERM Director was indisputable, he had put himself in a position of 'conflict of interest'.(12) Despite Bréchot's claim that his action was only inspired by his duty to protect patients, a priority for an INSERM Director, and that he was clearly protecting patients instead of his own family interests, the two Ministers urged him to resign. After Bréchot's resignation in October 2007, a mediation was set up by the Government which lasted eight months. The agreement was signed in June 2008 implying the cancellation of all legal procedures filed by Metagenex against public institutions (yet not the ones against Mr and Mrs Bréchot) and the transfer of the licences to Metagenex, which would be subject to its commitment to allow commercialization of only previously clinically validated ISET tests.

Despite the signed agreement, Lavergne's marketing of the non validated ISET cancer test to cancer patients is still ongoing and the manager of Metagenex continued to refuse to sign the contract with ANR. Instead, Metagenex' scientific advisor, Prof. Yvon Cayre, announced their intention to develop the *in vitro* culture of fetal cells isolated from maternal blood, a strategy that never proved successful in the literature due to the parallel proliferation of fetal cells from previous pregnancies and of non fetal cells. (13)

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Deaf and blind institutions

When the clinical validation of the ISET test for prenatal diagnosis of SMA

became public, parents at risk for this deadly disease asked to benefit from the new non invasive test. Surprisingly again, the implementation of the new test, even in a research setting, was hampered because of obscure problems “related to Metagenex”. This situation prompted CIANE to issue a motion and a press release in order to attract attention to this issue.(14)

On December 6, 2008, angry parents from the SMA risk group sent an open letter to President Sarkozy and to the Minister of Health, Mrs Roselyne Bachelot, complaining about the situation. Their letter remained unanswered even though CIANE’s intervention had been covered by an international Medical Press Agency.(15)

On December 19, 2008, CIANE urged Mr David Znaty to sign the ANR agreement allowing the funding of the clinical validation of the non-invasive prenatal diagnosis of Down syndrome. Their request yielded no answer. A few days later, the ANR announced that the project had been cancelled. Consequently, CIANE sent open letters to all parties involved in the partnership urging them to produce statements about their actual commitment, but only ANR replied with an elusive explanation.(16)

Meanwhile, Paterlini-Bréchot’s team had applied for funding from another source (PHRC, *Programme hospitalier de recherche clinique*) in order to validate the ISET test for Down syndrome. Their application was put in competition with a project from the same campus (*Necker Enfants Malades*) based on shotgun sequencing of free fetal DNA from maternal blood (Fan et al. 2008 and Chiu et al. 2008), an approach which, at variance with ISET, has never been validated for any genetic disease.(17)

Paterlini-Bréchot’s team proposed a comparative analysis of the two approaches (ISET and shotgun) in order to promote the most efficient approach. She was later informed that her application had been rejected. *In brief, the ISET method, which was prevented from being implemented, was then prevented to be funded arguing that “it had never be implemented”*.(18)

This fatal shot, as well as the funding by PHRC of the Necker project on shotgun sequencing of free fetal DNA, is consistent with the obstacles preventing the implementation of the clinically validated ISET test.

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A secret and untraceable contract

On March 3, 2009, CIANE sent an open letter to the Minister of Health urging her to take action in order to help the research on non-invasive prenatal diagnosis, with particular focus on Down syndrome. Again, no answer was given though various movements have been witnessed ‘behind the scene’.

A renowned independent medical journal (*Prescrire*) published a paper about CIANE(19) and invited the Coalition to write an article on this topic. (20) To this effect, an enquiry was launched. Letters were sent to the representatives of the Institutions owning the ISET patents asking for more details about the licensing contract.(21) Senior research leaders and health administrators such as Dr. André Syrota, Prof. Axel Kahn and Benoît Leclercq belong to the signatories. CIANE urged these members to hand

over the contract in full text or at least provide evidence of its registration with the National Institute of industrial property (INPI, *Institut national de la propriété industrielle*). Among signatories, only Axel Kahn replied three months later that *"the information should be sought from Metagenex"*…(22) In the meantime, INPI had confirmed that the contract was not registered, thereby putting these licenses under high risk of infringement.

On April 16, 2009, CIANE issued a press release along with an open letter to President Sarkozy.(23)

Again the letter was not answered but an increasing number of health professionals have now expressed their willingness to support CIANE's action for a clinical validation of the ISET test for Down syndrome.

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More battles yet to come

This story sounds unbelievable as we find it hard to evaluate stakes. Should we understand that private investors are so frantically in need for immediate profit that they ignore basic fair business practices to meet their ends? And that lobbying has more impact than relevant scientific achievements in public health? Has competition between scientists reached the point of taking any opportunity to eliminate one's rivals? Whatever the answers, there is no space on this battlefield for future parents and their specific needs.

Today, experts advocate the emergence of a regulated capitalism based on ethical frameworks. Far away from finance, the domain of science is still badly missing counter-power mechanisms that would allow the potential beneficiaries of innovations - also contributing as tax-payers - to be heard.

"Quality of life" progress for present and future generations still demands a reckless fight. As a matter of fact, Prof. Paterlini-Bréchot experienced police custody and faced a penal law suit transmitted directly from the public prosecutor to the judges without independent investigation. Despite the fact that she has been released by the Court, for her, biomedical research has become a very dangerous job.

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    1. *The ISET approach to detecting spinal muscular atrophy (SMA) and cystic fibrosis have been described in scientific publications since 2003 and 2006 respectively, but no report is available on their implementation as prenatal diagnosis;*
    2. *This means concretely that the method is not currently put in practice for parents at 25% risk of having another child suffering SMA or cystic fibrosis, and/or it has not been reproduced by other teams;*
    3. *Therefore this approach remains an interesting research method but I believe it is hardly applicable to the mass screening of Down syndrome, etc.*
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About the author

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Read also

- Metagenex : fin du conflit entre les découvreurs et les investisseurs d'un test dépistant des cancers. *Le Monde* (14 janvier 2010) *Metagenex: the end of the conflict between inventors and investors of a test for detecting cancer* (translation)