**National Consultative Ethics Committee for Health and Life Sciences**

# Opinion n° 99

## "in connection with a test (ISET-Oncologie) for the detection of circulating tumour cells in blood"

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**Persons heard:**

- on June 29th, 2007 Professor Patrizia Paterlini-Bréchot

- on July 5th, 2007 at CCNE, Professor Cayre, Dr. Wechsler and Mr. David Znaty, Société Metagenex

- and on Thursday September 6th, 2007 at CCNE Professor Cayre, Dr. Wechsler and Mr. David Znaty, Société Metagenex and Drs. Jean-Claude and Laurent Zerat, Laboratoire Lavergne

Professor Patrizia Paterlini-Bréchot, co-founder of Metagenex, referred to CCNE concerning the validation and marketing of test equipment for detecting the presence of circulating cancer cells in blood.
The referral was also addressed to INSERM's Ethics Committee (ERMES) which submitted a report on August 28th, 2007[1]. INSERM is itself a stakeholder in the patent together with AP-HP (*Assistance Publique Hôpitaux de Paris* - French public hospitals), the Descartes University (Paris V) and the inventor.
In view of the nature of the dispute opposing the parties on the distribution of their respective contractual rights and responsibilities for the validation and management of the patent for this test, CCNE viewed its competence in the matter to be marginal since the problem is essentially of a legal nature and *sub judice*. The Committee therefore considered that it was not in a position to comment on a specific case.

Nevertheless, CCNE wishes to take this opportunity of pronouncing itself more generally on the purely ethical aspects of the marketing and use of biological or cytological tests. If they are insufficiently validated and their use is extended to screening[2], they can produce results that are difficult to interpret and which might have harmful consequences on the psychological[3] and physical health of those undergoing the tests.

Since inventions and patents for performing or facilitating biological and cytological tests, such as the technique used by the ISET-oncologie project, are likely to become increasingly common, there is reason to fear that ambiguities in the interpretation of the rights and duties of parties to the contract may also become more frequent in the near future. The problem central to the referral therefore raises a more general issue: should not public health agencies be tasked with evaluating, not just the safety of marketed medicines, but also the reliability of diagnostic tests contributing to the decision to prescribe these medications? In view of the ambiguous interpretations, CCNE would like to suggest more precise definitions of the conditions in which new tests can generally be considered reliable and to formulate some recommendations to limit attendant risks (it being clear that part of these considerations are not pertinent as regards the ISET procedure which is not a test in itself but a tool to increase test sensitivity).

**1** Test validation. This implies a demonstration of the repeatability of results and a determination of sensitivity and specificity. In particular, ad hoc studies must clearly establish the correlation of test results with clinical data. (It must be noted that correlation may be statistical for a given population which is not exceptional. In this case, an in-depth analysis is required to determine the usefulness of the test for a particular

[1] http://www.inserm.fr/fr/inserm/organisation/comites/ermes/att00002074/avis_ermes_2808.pdf
[2] The equipment concerned by the referral operates in the following way: by filtering a sample of a few millilitres of blood through pores of a specific diameter, a very small number of cells of a size greater than those in normal cell populations can be isolated and then analysed. This test is called ISET-Oncologie (Isolation by Size of Epithelial Tumor cells; the word "Oncologie" refers to the pathology which it is meant to detect). The test does not provide a direct diagnosis which is the responsibility of a cytopathologist who also identifies the cells which were isolated. The machine does not diagnose; it merely makes diagnosis possible. Such detection would pave the way for earlier identification of certain metastatic cancers. The filtration system can also detect fœtal cells circulating in maternal blood. Prenatal applications are expected, i.e. diagnosis of chromosomal and genetic diseases (Down's syndrome and cystic fibrosis respectively).
[3] Psychological health in so far as they can cause anxiety with no possibility of relief by confirmation or rebuttal.

individual). In the sometimes ambiguous relationship between research and healthcare, and in the particular case of cytological tests, research to validate a test cannot obliterate the uncertainty intrinsic to any medical practice. Its principal aim is to limit uncertainty within acceptable limits. Such validation is absolutely essential in order to avoid obtaining results of dubious interpretation and therefore arriving at erroneous false positive or false negative diagnoses and prescribing inappropriate treatment or on the contrary abstaining when treatment is necessary. Marketing without validation could represent a serious public health risk and to be logical, should be subject to evaluation by an agency in charge of health-related issues such as *AFSSAPS* (French Health Products Safety Agency), HAS (*Haute Autorité de Santé* - French National Authority for Health) or the *Agence de Biomédecine* (Agency for Biomedicine). Such an institution should be given the opportunity of issuing an opinion as it must do before a medical drug is made available for sale. Until such an opinion is published, the Agency could at least make it known that it has not yet approved or so far examined the test at issue.

**2** Diagnosis is generally a step on the road to a medical decision, for either curative therapy or therapeutic abstention. The insertion of a cutoff between diagnosis and treatment is therefore usually artificial. Giving an opinion based solely on the concept of therapy, without taking into account the specificity and sensitivity of the diagnostic process leading to treatment, is ethically unacceptable.

The issue of availability to the public of a diagnostic test which has not been validated must not be limited to the question of reimbursement by the public health system. A physician's freedom to prescribe and everyone's right to practise self-medication or to use the internet to obtain the use of such equipment are also at issue. It is true that a number of diagnostic procedures with no validation are currently available without any kind of supervision by the healthcare agencies, in the name precisely of this freedom and the absence of public financing, but this situation is unacceptable as regards health protection when a serious medical condition is concerned[4].

**3** The evaluation required to validate such a test itself raises a major ethical issue. Cancer patients may consent to such research since they may feel that the highly rigorous oncological management they are provided with allows them to participate in research to fight a serious disease, but this is not the case for the general public. Is it possible to consent to research knowing that if results are divulged and are positive the participants themselves and their doctors will be put in a position of major uncertainty? What should be done with results? Only time (possibly several years or decades) can provide an answer regarding the true medical significance of the presence of these cells. The ethical complications of such research — although research on healthy volunteers and patients is already well regulated by the 1988 Huriet Law and its revision in 2004 — are self-evident. No less obvious, ongoing activity in this field is for the purpose of research , not of healthcare. Patients must be told that this is the case. Use for screening is therefore currently premature and would raise major ethical issues.

**4** All the ethical issues raised by systematic screening policies are becoming increasingly acute, be they related to genetic testing, the presence of abnormal fœtal cells in the mother's body, non-specific tumour markers or ever more sophisticated medical

[4] Clearly, defining a "serious medical condition" is difficult. However, there is an obvious difference between measuring an inflammatory condition by the examination of proteins for example — using a test that has never been validated — and tests identifying a cancer.

imagery. All these questions could well be amplified by the automated development and emergence of nanotechnologies. Cytological testing should therefore be included only exceptionally in a systematic screening policy.

**5** Encouraging the creation of joint public/private structures, which undeniably makes research more dynamic, is a legitimate objective. But economic advantage must not be allowed to supersede advantage in terms of public health and must therefore be scrutinised by an independent authority, such as HAS or AFSSAPS.

**6** Joint public/private structures may also raise a second level of ethical issues in connection with the nature of the control that an inventor may have the right or the duty to exercise on the use of, or possibly the abuse of, the product of his or her invention. It seems obvious that the holder of a patent can identify the possible risks or adverse effects linked to the use of his invention. In such an event, the inventor and the manager of the invention share responsibilities which must be clearly defined in order to avoid creating major conflicts of interest. Such a conflict may be present at the outset, if there is a personal financial involvement on the part of the inventor holding a patent as regards the development of the patent of which he is a co-holder, be it by an unforeseen risk or an adverse effect having possible financial consequences, or through the under evaluation at an ethical cost of such a risk in order to preserve profitability. The limitations on financial involvement for an inventor delegating all management responsibility to independent agents are apparent. Dissociation between the financial outcome linked to the possession of a patent and the management of that same patent should not, however, prevent the creation of a start-up. But the respective responsibilities of everyone concerned, inventors and managers both, must be clearly established as for that matter the Law provides in Article 25.2 (see Annex 1) of the 1999 law on Innovation and Article 17 (see Annex 2) of the law dated April 18, 2006. Furthermore, inventors must not retain any responsibility as regards management or economic and commercial negotiation. Their involvement is governed by a Consultant's contract, the terms of which are approved by ethical authorities in the institution in which they are employed. They may however sit on the company's scientific and medical board. CCNE seizes this opportunity of emphasising that in order to preserve ethical principles, conflicts of interests of this nature must be submitted to bodies such as HAS or AFSSAPS.

**Recommendations**

Consequently, CCNE recommends:

- That evaluation by a national health authority (HAS, AFSSAPS or the *Agence de la Biomédecine* should be a mandatory preamble to the marketing of any test or process for diagnosis, regardless of conditions governing reimbursement of the purchase price to the buyer by national health authorities. Informing the public that the medical applications of an invention have not been evaluated should be made mandatory;

- Should it be difficult, for legal reasons, to exercise control over tests that have not yet been officially approved, are not reimbursed by the national health system and are eligible for unrestricted sale, the independent Agency should at least make it mandatory to include specifically for the use of the person taking the test (and not just as part of the patient information leaflet as is the case for other products which are a

potential health risk but are marketed without restriction) an explicit warning making it clear that the test does not comply with all the conditions for evaluation and validation necessary for a reliable interpretation of the test results which it may produce and cannot therefore be in any way guaranteed by public health authorities;

- That a clear distinction be made between research and therapy, in particular by patient support groups[5], so as to avoid a situation where the use of techniques becomes inevitable simply because they exist and not because of what they can do. The development of a technical tool is not an end in itself, independently of the use to which it is put. In other words, to abstain from reflecting on the use to which the results of a diagnostic test will be put, be they positive or negative, is a regrettable current trend and a source of increasingly serious complications. Techniques do not dictate the conditions of their own use. That is why the involvement of existing and competent structures, which are independent of the manager, the user, the research institute, the inventor and of patients themselves (HAS, AFSSAPS and Agence de la Biomédecine) are so important to build up trust in the use of biotechnology;

- That should the case arise, authors of an invention for biomedical purposes inform users that the use of their invention is still part of a research process that will not be entirely validated as long as the results of an independent evaluation are not available and made known to the public;

- That conflicts of interest between inventors and shareholders be clearly identified and stated. The management of the company must be totally independent of the inventor-shareholders so that the latter are not the object of any suspicion of ambiguous participation (as already stated in the 1999 law on Innovation which stipulates that inventor-shareholders must not be part of the company's management structure, even though the original 15% limit in the 1999 law was raised to 49% of the capital in the new 2006 law);

- That finally those to whom the test is proposed be clearly told of the remaining uncertainties concerning the actual significance of the presence of one or several circulating tumour cells. It is the task of the person prescribing to make this known and to be fully aware that the issues arising in a screening process are very different from those involved when performing a medical examination

Thursday September 13, 2007

[5] With a view to promoting the provision of information which can dispel any risk of confusion between exploratory and validated test procedures, patient support groups must be regarded as preferred contacts. If they are given precise data on the nature of tests on the market, they will be able to play an effective role to enhance vigilance and relay information to the public.

## Annex 1

### Law n° 99-587, dated July 12, 1999 on innovation and research, article 25.2

"Art. 25-2. - For a renewable period of five years, government officials defined in the first paragraph of article 25-1 may contribute scientific expertise to a company developing the results of their research accomplished in the course of their official functions when that company is implementing a contract signed with a public entity or corporation.
"The conditions governing the provision of scientific expertise by that official are defined by an Agreement between the company and the public entity or corporation designated in the first paragraph. The conditions must be compatible with full discharge of the official's public duties.
"The official may also be authorised to own stock in the company, within a 15% limit, on the condition that in the five previous years, he has not exercised in the course of public or official duties, any control over the company or participated in the establishment or signing of contracts between the company and a public research organisation.
"The official may not participate in the establishment nor in the letting of contracts and agreements between the company and a public research organisation. Within the company, he may not discharge management or executive functions.
"The authority to whom the official reports will be kept informed of the income the official receives as a consequence of the stock he owns in the company, of any sale of securities he may engage in as well as of any other remuneration, within a limit set by decree, provided for by the Agreement mentioned in the second paragraph.
"The Commission mentioned in the third paragraph of Article 25-1 is kept informed for the duration of the authorisation and for a period of five years after expiration or withdrawal of any contracts and conventions concluded between the company and the public research organisation. Should the Commission consider that the information reveals an offence against the material or moral interests of public research policies, the Commission must notify the Minister with authority over the public legal body concerned.
"Authorisation is delivered and renewed by the authority employing the official after approval by the Commission mentioned in the third paragraph of Article 25-1 as stipulated in the conditions outlined in paragraphs three to six of this article. Authorisation is withdrawn or not renewed if the conditions that presided over its delivery have ceased to apply or if the official does not comply with the present article. In that event, the official must dispose of his assets in the company within a year, after which he may no longer own, directly or indirectly, any interest in the company. He may only continue his activity within the company in the conditions set out in the first paragraph of Article 25-1."

## Annex 2

## PROGRAMME law n° 2006-450 dated April 18, 2006 on research

### Article 17

Chapter III of Title I of Book IV of the Code on Research is modified as follows:
1° The following paragraph is added to Article L. 413-1:

"The contract mentioned in the first paragraph is concluded within a time period specified by decree. Failing compliance, the authorisation granted to the official lapses.";

2° In the second sentence of the last paragraph of Article L. 413-6, the wording: "within a 15% limit of the capital "is replaced by the following wording: "within a 49% limit of the capital giving rise to a maximum 49% of voting rights";

3° After the first paragraph of Article L. 413-8, a further paragraph is added as follows:

"The contract mentioned in the first paragraph is concluded within a time period specified by decree. Failing compliance, the authorisation granted to the official lapses.";

4° In the first paragraph of Article L. 413-9, the wording: "within a 15% limit" is replaced by: "at the time of its creation or at a later date, within a limit of 49% of the capital giving rise to a maximum 49% of voting rights";

5. The first two sentences of Article L. 413-11 are replaced by the following three sentences:

"The authorisation is granted by the authority employing the official after approval from the Commission mentioned in the first paragraph of Article L. 413-3, in accordance with the conditions outlined in that same Article. Should the conditions prevailing at the time of granting authorisation cease to apply, the same Commission's approval will be required for a renewal. Authorisation is withdrawn or is not renewed if the conditions prevailing when it was granted no longer apply or if the official fails to comply with the provisions of the present section.";

6° The second sentence of the first paragraph of Article L. 413-12 reads as follows:

"Their participation in the stock of the company may not exceed 20% nor give rise to over 20% of voting rights.";

7° The first two sentences of Article L. 413-14 are replaced by the three following sentences:

"Authorisation is granted by the authority employing the official after approval by the Commission designated in the first paragraph of Article L. 413-3, in accordance with the provisions in the said Article. If the conditions prevailing at the time authorisation was granted cease to apply, the said Commission's approval is required for renewal. Authorisation is withdrawn or is not renewed if the conditions prevailing when it was granted no longer apply or if the official fails to comply with the provisions of the present section."