

## Biomarker Discovery, Development, and Implementation in France: A Report from the French National Cancer Institute and Cooperative Groups

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### Abstract

Biomarkers are increasingly changing the medical practice in oncology. One of the major challenges in the field of personalized medicine or biologically adapted therapies is to ensure a rapid and extensive implementation of emerging biomarkers as soon as proof of their medical usefulness is obtained. A special program has been developed in France to facilitate the assessment and use of biomarkers. The French National Cancer Institute has set up a total of 28 laboratories in public hospitals to perform biomarker testing for clinical use. This program is enabling all patients who present with cancer to receive free testing for biomarkers, such as K-Ras, epidermal growth factor receptor, c-Kit, and Braf mutations. Funding for these laboratories comes from the French Ministry of Health. The future of these laboratories includes the development of DNA arrays and multiplex technologies for clinical use. Toward that end, the French National Cancer Institute is financing several large clinical trials that several large clinical trials are currently evaluating the feasibility and medical utility of DNA arrays and next-generation sequencing in the context of academic centers. The programs are being run by cooperative groups. *Clin Cancer Res*; 18(6); 1555–60. ©2012 AACR.

### Introduction

Recent advances in biology and the rapid development of biotechnology have allowed the discovery of biomarkers that can predict for cancer outcome and help determine the best use of new drugs. For several years, the development of such biomarkers was limited by the lack of recommendations as to how their usefulness should be evaluated and which level of evidence should be required for their use in practice. Recent progress and the achievement of some consensus in this field are speeding up the identification of new biomarkers (1–3). Despite these global advances, however, some major discrepancies still remain among countries regarding the use of such biomarkers.

France has a social medical system in which the state covers the cost of all cancer care. The field of cancer research was boosted in 2003 by the development of the first Cancer Plan and the creation of a national agency in charge of coordinating quality of care, public health, and research, the French National Cancer Institute (NCI). The Cancer Plan

specified priorities in the management and study of this disease. An update of this plan was launched in 2009 by French President Nicolas Sarkozy. Two of the major objectives of this update were to accelerate translational research and decrease inequities in cancer care.

In this review, we describe the tools that have been put into practice in France in order to allow free and wide access to biomarkers for the French population.

### Biomarker Implementation

#### Biomarkers for daily practice: process for approval and reimbursement

Overall, the regulations regarding approval of a biologic test are less stringent in France than in other countries, such as the United States. In France, biomarkers for therapeutic use can be employed as soon as approval has been granted by the European Union (CE-IVD label). Moreover, until recently, no specific certification was required for laboratories that perform biomarker analysis for clinical use. As an illustration, no equivalent of the Clinical Laboratory Improvement Amendments certification was necessary for the different medical laboratories to provide results. Nevertheless, new legislation was recently approved (law number 2009-879, July 21, 2009; ordinance number 2010-49, January 13, 2010) that makes it mandatory for all laboratories to obtain an accreditation before 2018, to be able to continue performing these tests. Reimbursement by health insurance requires further approvals and is usually a lengthy process. To address this limitation, 2 processes have been put into practice: First, the French Ministry of Health is providing a yearly grant to public hospitals to

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perform a limited number of biomarker analyses that do not need to be submitted for reimbursement, including BRCA mutation status, MGMT testing, and several other genetic tests. Second, the French NCI is also funding a total of 28 laboratories whose mission is to perform tests for predefined genomic markers that are particularly linked to predict sensitivity to targeted agents, as explained below.

#### Development of public laboratories to ensure wide access to new predictive biomarkers

To decrease the disparities in access to biomarkers and ensure the prompt implementation of biomarker testing in daily practice, the French NCI has developed a network of 28 laboratories for molecular testing in public hospitals, built on the strong expertise of French hospitals in the field of biomarkers. Each laboratory is located in a specific geographic area and is expected to offer free molecular testing to the nearby population for both private and public centers. This initiative started in 2006 with the investment of €4 million to structure these laboratories. In 2010, funding was provided by both the French NCI (€3.5 million) and the French Ministry of Health (€8.5 million). A total of 144,000 tests were performed in this network of laboratories in 2010, including 50,000 designed to predict efficacy of a targeted agent. This structure, whereby the NCI leads a small number of laboratories, allows (i) easy communication among the different laboratories, (ii) rapid implementation of new technologies, (iii) high-quality testing, (iv) prompt access to personalized medicine for cancer patients, and (v) the development of a large national molecular database to run research programs. A list of the different tests performed in these laboratories is provided in Table 1. The French NCI is also responsible for the addition of a new biomarker in the list based on recommendations provided by an external panel of experts. Uniformity of the technical and analytical procedures is confirmed through yearly meetings and cross-validation programs. When the sensitivity of detection matters, some recommendations are being provided by the French NCI;

for example, in the case of K-Ras, a 10% sensitivity for detection is recommended.

Testing for K-Ras and epidermal growth factor receptor (EGFR) provides a good illustration of this organization. In May 2008, the European Medicines Agency (EMA) approved the use of cetuximab (Erbix; Merck KGaA) and panitumumab (Vectibix; Amgen Inc.) only in patients with wild-type K-Ras colorectal cancers. At the end of 2008, the French NCI allocated €2.5 million in the 28 laboratories to run the tests. In 2010, about 16,500 K-Ras mutation tests were performed. The story is similar for EGFR testing. In June 2009, the EMA approved gefitinib (Iressa; Astra Zeneca) for patients with activating EGFR mutations. At the end of 2009, the French NCI approved €1.7 million for the 28 laboratories, and a total of 17,000 EGFR mutation status results were provided in 2010. Figure 1 shows the geographical location of these 28 laboratories and the volume of K-Ras/EGFR tests performed. Regarding the number of tests done for hematologic malignancies in 2010, the 28 laboratories performed 13,634 tests for JAK2 V612F mutation, and 23,849 quantifications of BCR-ABL transcripts. The mean time for the oncologist to receive the results was 13 days. Pathologists who send the samples are reimbursed for their fees. Each of the 28 laboratories is performing the whole panel of genomic tests described in Table 1.

The development of this network of molecular laboratories is the first stepping-stone in the public personalized medicine program. All of the biomarker tests in this program are being performed with a single gene assay. The evolution of personalized medicine in the cancer field is clearly going toward a higher number of biomarkers per patient and the use of more-complex (i.e., multiplex) bioassays. To address this complexity, several programs have already started to assess the feasibility of implementing DNA arrays and next-generation sequencing (NGS) into daily practice.

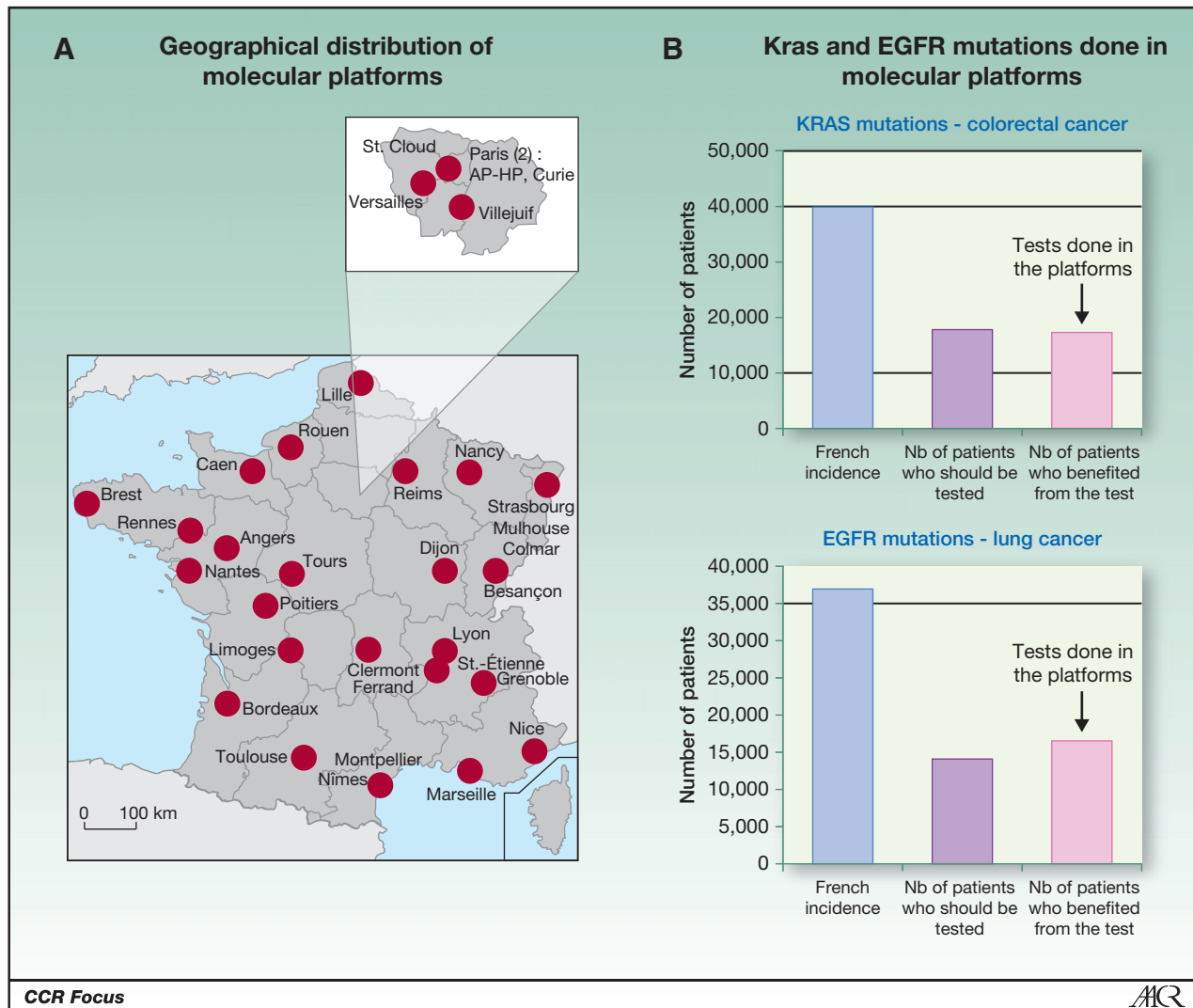
#### Development of DNA arrays and NGS for daily practice

The use of arrays offers the theoretical advantage of allowing several markers to be assessed in a single test. The

**Table 1.** Biomarkers tested in the 28 public molecular laboratories

Molecular alteration	Disease	Indication
BCR-ABL translocation	Chronic myeloid leukemia/acute	Imatinib prescription
BCR-ABL detection	lymphoblastic leukemia	Imatinib prescription
BCR-ABL quantification		Monitoring of minimal residual disease
ABL mutation		Resistance to imatinib
KIT and PDGFRA mutations	Gastrointestinal stromal tumor	Imatinib prescription
HER2 amplification	Breast and gastric cancers	Trastuzumab prescription
KRAS mutations	Colorectal cancer	Panitumumab and cetuximab prescription
EGFR mutations	Lung cancer	Gefitinib and erlotinib prescription
EML4-ALK translocations	Lung cancer	Crizotinib prescription
BRAF mutation V600E	Melanoma	Vemurafenib prescription

Abbreviation: PDGFRA, plate-derived growth factor receptor  $\alpha$ .



**Figure 1.** Development of 28 public molecular laboratories in France for molecular testing. A, the geographical distribution of the 28 laboratories. B, the volume of K-Ras and EGFR tests done in the laboratories. In B, the incidence is the overall number of cases per year, regardless of stage, and the number of patients who should be tested is an approximate evaluation of patients who are presenting with a metastatic disease. This approximate evaluation may explain why the actual number of patients tested is higher for lung cancers. Adapted from the French NCI Scientific Report 2010–2011 with permission from the Institut National du Cancer (15).

application of this technology in daily practice could avoid the need to set up a new test for each new biomarker and could allow for a more reproducible result. To explore the potential use of arrays in standard practice, prospective trials have been launched to explore the potential use of arrays in standard practice. The designs of 2 of these trials, REMAGUS04 [Standard Neoadjuvant Chemotherapy Versus Genomic Driven Chemotherapy in Patients With Breast Cancer (4)] and SAFIR01 [Screening Approaches for Individualized Regimen 01(5)], are summarized in Fig. 2.

The REMAGUS04 trial (4) is a prospective study of 300 patients with breast cancer who were randomized to receive either standard neoadjuvant chemotherapy or a genomic-driven chemotherapy. The primary endpoint was efficacy of the genomic-driven chemotherapy. Of

interest, the secondary endpoint was the implementation of gene expression arrays in daily practice. In this trial, all samples were profiled using Affymetrix U133plus2 (gene expression array) and results were available within 15 days. This study was coordinated by the Remagus cooperative group. Enrollment has been completed and results will be presented soon.

The SAFIR01 trial (5) is also a prospective study that aims to determine whether comparative genomic hybridization (CGH) array and sequencing of *PIK3CA* and *AKT* will enable investigators to direct patients into specific clinical trials. This trial is already open for recruitment and is expected to include 400 patients with metastatic breast cancer (as of January 2012, 200 patients had already been enrolled). Molecular analyses are performed from fresh

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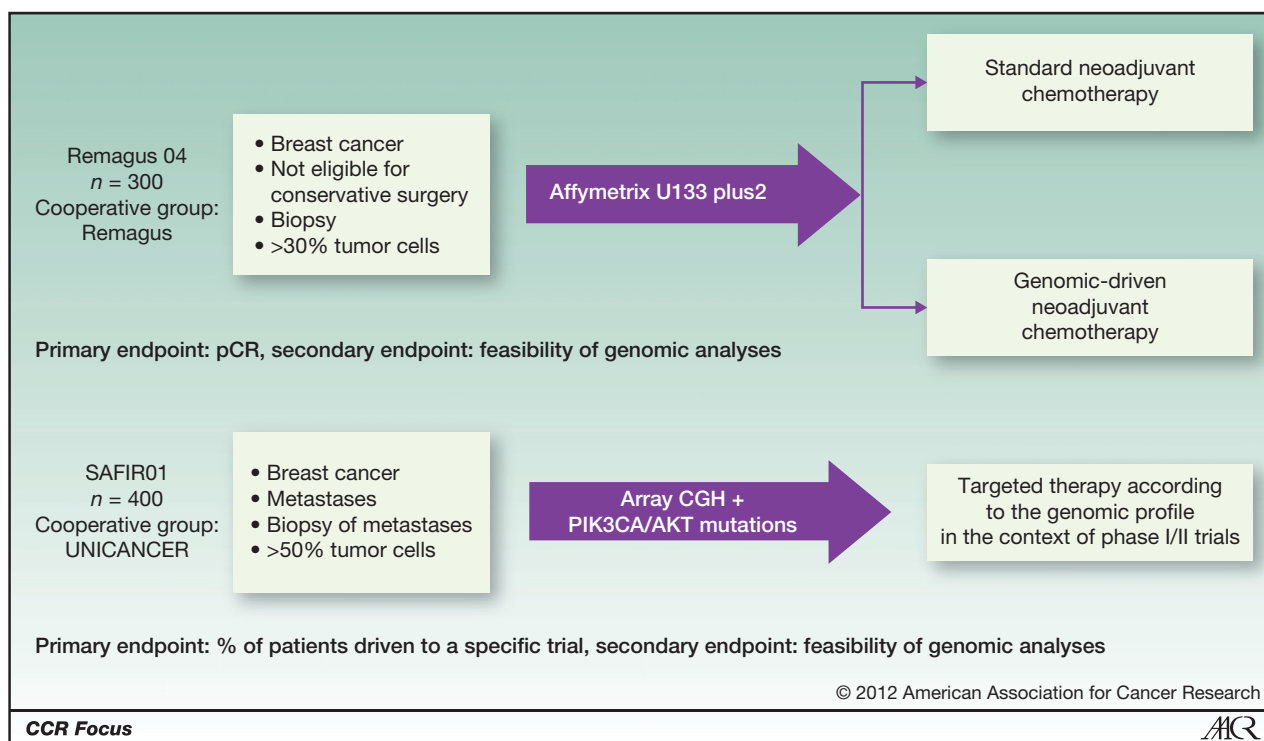


Figure 2. Clinical trials supported by French NCI testing implementation of DNA arrays. This figure describes 2 trials that aim to evaluate whether gene and CGH arrays are feasible in the context of daily practice. The goals are to develop infrastructures for performing arrays in the context of daily practice and to evaluate whether these technologies are feasible. pCR, pathologic complete response.

biopsies from a metastatic site. Four genomic laboratories are running the samples using 2 different arrays (Affymetrix 6.0 SNP and Agilent 180K). This study is sponsored by UNICANCER and funded through French NCI grant call.

These 2 trials illustrate the efforts to implement DNA arrays in standard clinical practice. If these studies and others succeed in showing that this approach is feasible for academic centers, then their cost-effectiveness will need to be examined within the context of large validation studies with specific funding. The mid-term vision would be to integrate DNA arrays in some of these 28 laboratories, and to offer multiplex testing to patients for free.

Several local initiatives are being taken to implement NGS for daily practice. The Curie Institute, with a grant of €12 million from the French government, is developing the CIGex program. In this program, the hospital plans to use NGS in the context of a prospective trial to identify potential molecular targets at the patient level. The Gustave Roussy Institute, with the support of private funds, is developing a similar approach. In the latter program, investigators will use Ion Torrent technology in a prospective study with the initial goal of testing 500 genes for each patient. Overall, 600 patients are planned to be included in this prospective trial. Each mutation of interest will be validated by the Sanger method. The scale-up in terms of gene numbers will depend on the results of this first step. The decision by the French NCI to develop NGS at the national level will be taken after the feasibility of the technology has been shown

in these trials and the expected cost/benefits have been evaluated.

**Perspective from biomarker companies in the French system**

The business model for biomarker companies in France is clearly different from that in other countries. This is related to the fact that public hospitals have the capacity and are willing to run the molecular analyses. Biomarker companies can develop 3 different strategies. First, a company can develop and sell kits to the laboratories for them to run and interpret the test results. This is the model employed by Ipsogen, which developed a genomic-grade reverse transcriptase PCR (RT-PCR) that is aimed at being performed in each laboratory (6). In the second strategy, the molecular analysis could be done in each hospital, but the company would interpret the results. This is particularly relevant when a bioinformatic analysis is required. This theoretical model has no precedent in France but could be developed if the use of arrays is implemented. In the third model, a central laboratory led by a biomarker company would both perform the test and analyze the results. Although this model has been widely developed in other countries, there is no equivalent in France. Nevertheless, several initiatives are being undertaken in France to implement Oncotype DX (7) with this model.

Overall, the optimal business strategy for biomarker companies in France still needs to be defined. This special situation in which academic centers run high-level

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molecular analyses for daily practice is clearly challenging the model in which a private central laboratory runs the molecular analyses.

**Research on Biomarkers**

**Funding**

Funding for biomarker research usually comes from 3 sources: charities, public research agencies, and the French NCI. The most important donation is coming from the French NCI. Biomarker research can be funded by 6 different grant calls, as summarized in Fig. 3. These grant calls cover research ranging from basic science (i.e., when the concept is discovered) to the last step of validation. The part that is specifically related to translational research funded 66 projects in the last 4 years, for a total of €25 million.

In the last 2 years, the government has made a specific investment in research infrastructure (not only for cancer) called Investissements d’Avenir (Investments for the Future) with an overall budget of €35 billion. The main goal is to generate high-level strategies that will be competitive at an international level. This has allowed the development of several large projects for cancer research. For example, the ICGex, led by the Curie Institute, has been granted €12 million to set up laboratories for arrays, including NGS. The protocol known as CANTO (CANcer Toxicities) is another example, led in this case by UNICANCER. This cohort will include 20,000 women with early breast cancer and will focus on the development of predictors for treatment toxicities. It has received €13 million from the French government.

**Organization of translational research within cooperative groups**

French cooperative groups have traditionally performed practice-changing clinical trials to test a drug in a large population (8). These groups have also created a specific organization for translational research. Within each clinical study, a steering committee decides about a number of primary molecular analyses that are considered to be strategic. They usually consist of arrays, tissue microarrays, and validation markers. Once these analyses have been performed, the steering committee calls for projects to be conducted by the different groups involved in the protocol (investigation centers). Once these centers have replied to these project calls, the remaining material is open for external collaboration led by centers that have not participated in this particular clinical trial. Finally, because sample collection and storage is a key issue (9), all samples collected and stored by all projects sponsored by UNICANCER are centralized in a single biobank at the Centre Leon Berard in Lyon for more-effective biomarker research. In similarity to their U.S. counterparts (10–12), the translational research committees of the French cooperative groups also aim to prospectively evaluate the medical usefulness of biomarkers and to use arrays or NGS to guide treatment decisions.

**A specific program: Tumor ID Cards**

The Ligue Contre le Cancer (League Against Cancer), a French charity, recently started its own large research program, entitled Cartes d’Identité des Tumeurs (Tumor ID

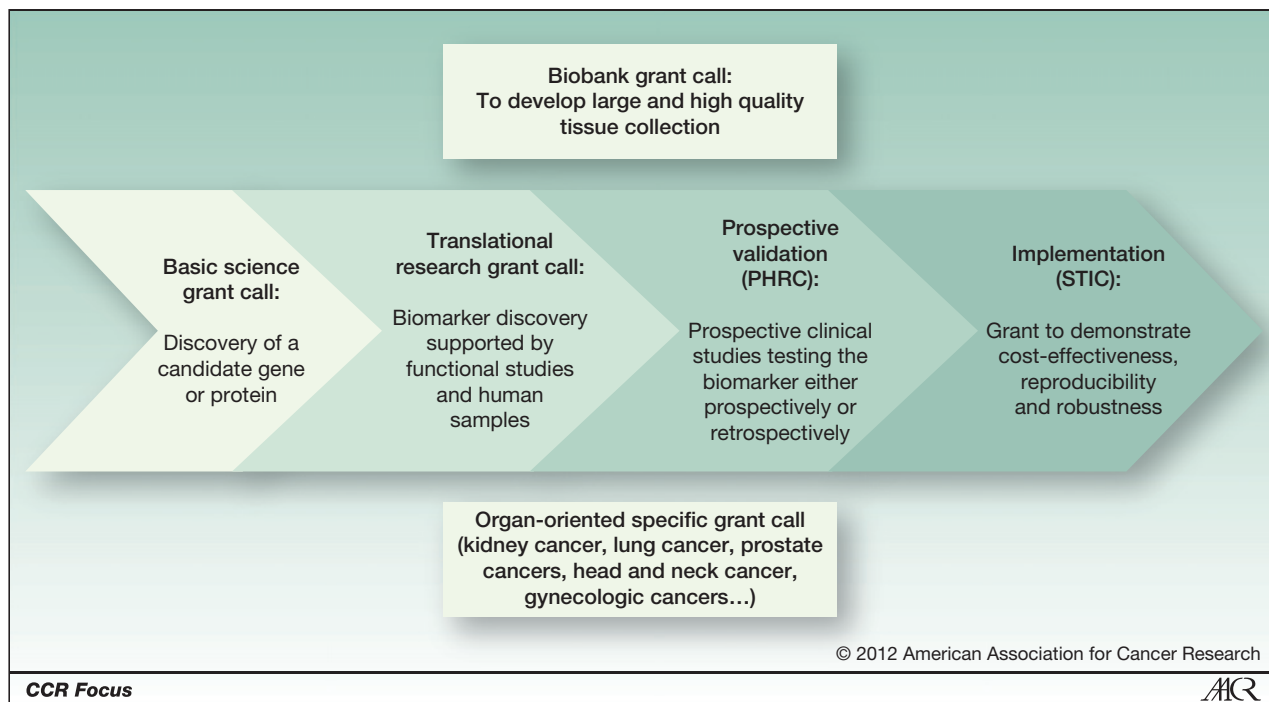


Figure 3. Grant calls from the French NCI to support biomarker research in France. PHRC, Programme Hospitalier de Recherche Clinique; STIC, support for extensive and innovative technologies.

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Cards). This program is built on a standardized process and uses arrays with a network of more than 60 teams of researchers, pathologists, doctors, and bioinformaticians. It is also supported by the French NCI and offers one of the largest tumor databases in Europe. Since its implementation, more than 9,000 annotated tumor samples and 12,000 microarray experiments have been performed to characterize more than 13 different types of tumors (13). As an illustration, this program recently enabled investigators to refine the molecular classification of breast cancer (14).

### Conclusions

The main goal of the French model for biomarker implementation is to provide all patients with free access to the main predictive biomarkers. Toward that end, the French NCI has developed a network of 28 laboratories located in

public hospitals. One of the objectives of this model is to save expenses related to drug costs by providing the drug only to a subset of patients who are expected to benefit the most. The other goal is to ensure that French citizens have access to biomarkers and drug innovations. This objective has already been reached, because it is now considered that each French patient has free access to predictive biomarkers and their companion drugs. The next step will be to implement multiplex technologies in order to increase the number of biomarkers that can be tested for each patient.

### Disclosure of Potential Conflicts of Interest

F. Andre is one of the inventors of the patent that led to the development of the Dx14 test. No other potential conflicts of interest were disclosed.

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