MIND THE GAP !

Working together to set research priorities for NASH
with an optimal contribution of biobanks

King Baudouin Foundation
Working together for a better society

Belgian Association for the Study of the Liver

BBMRI.be
Biobanking and BioMolecular resources Research Infrastructure Belgium

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COLOPHON

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Cette publication est également disponible en français sous le titre: Définir ensemble les priorités dans la recherche sur la NASH avec une contribution optimale des biobanques
Deze publicatie bestaat ook in het Nederlands onder de titel: Samen prioriteiten bepalen voor het onderzoek naar NASH met een optimale bijdrage van biobanken

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INTRODUCTION

Research is both useful and necessary. But are the subjects of research sufficiently in line with the real needs of the end users – patients and families, healthcare providers, insurers, public authorities, companies etc.? Too often the programme is determined by the researchers and the funders, with no one else entitled to have their say. With "Mind the Gap", the King Baudouin Foundation would like to correct this imbalance.

Based on the methodology from organisations like the James Lind Alliance (GB), the University of Amsterdam (The Netherlands) and the Fondation Motrice (FR), the King Baudouin Foundation organised a seminar in November 2015 entitled "Priority Setting in research through multi-stakeholder dialogue", which generated 3 pilot projects in different areas of healthcare:

- liver diseases and biobanks;
- Tuberous Sclerosis or Bourneville's disease, a rare genetic disease;
- return to work after a long period of work incapacity.

Each of these projects is described in a publication of the series 'Mind the Gap!'.

Fixing research priorities through dialogue with all the concerned parties: this would seem as simple as it is obvious. But, in fact, the process of dialogue is very rarely applied and remains a delicate balancing exercise between a multitude of voices and interests.

However, it is well worth the trouble. When the "forgotten" parties are given a voice, new issues, still unanswered, are quick to emerge, members of the public, patients, but also professionals, become more involved in the research, the ways and means are more effectively used and the results of the research have a correspondingly greater impact.

The NASH & BIOBANKS project which, like the two others, was based on dialogue with and between all the parties involved - patients (whether represented or not by associations) and families, doctors and caregivers, researchers and universities, pharmaceutical and biotechnology companies - had the **triple objective** of:

1. **prioritising, through multi-stakeholder dialogue, present and future research topics regarding NAFLD (non-alcoholic fatty liver disease) and NASH (non- alcoholic steatohepatitis), for which biobanks can be a decisive asset;**

2. **identifying the challenges which will confront biobanks in the future taking account of the views of the various parties involved;**

3. **contributing in this way to the establishment of a long-term evolutionary dialogue.**

For those who are acquainting themselves with this project, the combination of NASH and biobanks may be disconcerting. First of all, what exactly is NASH? And biobanks, what use are they? Even if liver disease is nothing new to you, the connection with biobanks is not at all obvious. And no matter how interested you might be in their collection of samples of human origin, their usefulness in the fight against the epidemic of "fatty liver" and NASH will not be immediately clear to you.

However, there is no longer any time for procrastination. Declared in 2016 by researchers at the Howard University of Washington to be "the next global epidemic", NASH has already crossed the frontiers of the wealthy countries and continues its progression world-wide. The First International NASH Day which, on 12 June 2018, brought together doctors, scientists and patients in over 25 large towns throughout the world for a day of action against this dangerously silent disease, raised the alarm about the urgent nature of the problem. This urgency was again reaffirmed in the appeal for mobilisation launched by 150 international experts in the area of metabolic and liver diseases: "Our objective is to ensure that NASH becomes a subject of serious interest in the general mass media and a regular subject of discussion in society and that it is recognised by the public health authorities as one of the major challenges for the years and decades to come. We consider this approach as an integral part of our social and societal responsibilities".

In one-and-a-half year of considerations, discussions and research, the NASH & BIOBANKS Priority Setting project has demonstrated that this social and societal responsibility extends to all of us. This is the first conclusion of this report, which develops the results of the dialogue process concerning NASH research priorities and the way in which biobanks can contribute to this research. It represents a call for the development of research on the major public-health challenge that NASH represents as well as an encouragement to continue the dialogue between the biobank stakeholders. The biobanks must obviously be considered, given the urgency of the matter and collective nature of the responsibility, as a common indispensable research asset.

This project could only be realised thanks to the contribution of motivated citizens and professionals. We thank them for their commitment!

Chapter 1. Liver diseases

The liver, which is the largest gland in our body – it weighs between 1.4 and 1.6 kilos – is a vital organ, fulfilling three functions which are essential to our health.

1. **Detoxification:** the liver is a true filter, which recovers and eliminates large quantities of toxins present particularly in our food and drink.

2. **Synthesis:** the liver ensures the metabolism of carbohydrates, lipids and proteins, while also secreting bile which is essential to digestion. In addition it prevents haemorrhages due to a coagulation process.

3. **Storage:** the liver is a reservoir of vitamins A, D, E and K. It also plays a fundamental role in blood sugar regulation, because it is programmed to store and redistribute significant quantities of glucose in the body.

> *"There is not just one liver disease, there are a multitude of them, some frequent, others less so. Why are we focused on them? Because they are diseases that often end badly after years of a life with diminished quality. Can they be of interest to both the general public and the decision makers? When one realises that, just in the European Union, 30 million people at present are suffering from chronic liver disease, the answer would seem obvious!"*
>
> Professor Peter Stärkel, liver specialist, UCL Saint-Luc

Although it has a remarkable ability to regenerate itself, the liver is far from invulnerable. At the most recent count (2010), liver cancer caused over 780,000 deaths each year in the European Union. It is generally the result of cirrhosis, a chronic liver disease which may be caused by an excessive consumption of alcohol, but also by the hepatitis C virus, the non-alcoholic fatty liver disease (NAFLD) and other rarer diseases, such as primary biliary cholangitis.

HEPATITIDES: GREAT STRIDES IN TREATMENT

Hepatitis C is transmitted through blood, blood products and (not properly disinfected) material which has been in contact with blood. Since 1990, blood bags intended for transfusion are systematically checked for the hepatitis C virus, but they are still dangerous because the virus can remain somnolent in the body, completely unsuspected, for years, even decades. Result: in Belgium alone, 100,000 people at least are carriers and over 50% of these do not know that they are.

Despite the seriousness of hepatitis C, however, the 'Liver disease & biobanks' project did not concentrate on this. Not only because every donation of blood now undergoes screening which reduces the risks of contamination, but also and above all because, recently, hepatitis C has benefited from a real treatment revolution. New combinations of medicines, put together according to the profile of the patient and the characteristics of the virus, achieve a complete cure in 90% to 95% of cases, as the virus, which is prevented from multiplying, is eliminated by the immune system. Furthermore, the treatment, which uses two or three molecules but is limited to one or two tablets per day and lasts for a maximum of twelve weeks, is practically without side effects. At the present time only the most seriously affected patients are benefiting, but starting from 2021 it should be available on the National Health System (RIZIV-INAMI) to all carriers of the virus.

Hepatitis C is close to being overcome and the other hepatitides are much less dangerous: Hepatitis A, or travellers' hepatitis, against which there is a vaccine, disappears spontaneously in 99% of cases; hepatitis B, against which there is also a vaccine, becomes chronic in 10% to 15% of patients but the treatment is effective even if it has to be continued for life; hepatitis D, caused by a co-virus, only infects the body in association with the hepatitis B virus; and hepatitis E, linked to the consumption of wildfowl and shellfish, usually disappears spontaneously although it can develop a severe form in pregnant women.

NASH: A SILENT EPIDEMIC

Cirrhosis and its corollary, liver cancer, should therefore be on the decrease. This, however, is not the case. The reason is a new risk factor which is increasingly involved in cirrhosis: NASH (non-alcoholic steatohepatitis). The participants in the multi-party dialogue decided to concentrate on this disease based on the criteria given below.

A rational choice

How can a judicious choice be made among the pathologies involved in order to optimise the contribution of biobanks to liver research? In answering this question, the participants in the multi-party dialogue listed a certain number of criteria:

- diseases having a crucial effect on the patients' quality of life;
- diseases already prevalent today but which may increase in importance in the future and therefore seriously affect future generations;
- diseases affecting a large number of people;
- diseases which are very costly for society;
- diseases for which facilitation and/or acceleration of diagnosis would be decisive;
- diseases which could benefit from research;
- diseases in which biobanks could play an active and even determining role.

In this context, the choice of NASH was imperative.

But what is NASH? To define it, a silent epidemic must be mentioned, an epidemic about which most of our contemporaries know nothing, not even the fact that quite a few among them are already affected by it: fatty liver.

Non-alcoholic fatty liver (commonly known by its English acronym **NAFLD**, for **Non Alcoholic Fatty Liver Disease**) is a disorder characterised by an excessive accumulation of lipids in the hepatic cells. In other words the cells of the liver literally gorge themselves on fat. The prevalence of fatty liver is estimated at between 20% and 25% world-wide. In the European Union, about 116 million people may suffer from it.

> *"NASH is found in the same context as obesity, hypertension, diabetes and dyslipidaemia. A context dominated by bad food and a sedentary life-style. To put it another way, it is disease of civilisation."*
>
> Professor Peter Stärkel, liver specialist, UCL Saint-Luc

"Suffering from" is not the ideal expression, though, because fatty liver generally develops insidiously: for a long time its victims are unaware of any symptom, and even hepatologists, faced with blood tests which are practically normal and ultrasound examinations giving little information, admit that they cannot determine with any degree of certainty whether a patient is at risk.

At risk of what? In itself fatty liver is not dangerous, but 30% of those affected with fatty liver present a high risk of non-alcoholic or metabolic steatohepatitis (commonly known by its English acronym **NASH**, for **Non Alcoholic SteatoHepatitis**), characterised by an inflammation of the liver and degeneration of the liver cells. Patients may then develop progressive liver fibrosis or continue towards cirrhosis and/or liver cancer.

While the detection of lesions due to NASH requires a liver biopsy, fatty liver can be diagnosed less invasively with medical imaging. At present, unfortunately, it is impossible for the hepatologist to distinguish between patients who will live for many years in complete harmony with their fatty liver and those whose health will very quickly deteriorate. In addition, although several possible medications are undergoing clinical trials, there is not yet any medical intervention which might reverse the course of the disease. To escape permanently from the threat, the fatty liver patient must radically change his/her way of life and eating habits, possibly even with the help of bariatric surgery (such as a gastric band).

Important to know

- In the EU, 30 million people suffer from chronic liver disease.
- Each year, world-wide, a million people die of cirrhosis of the liver and 750,000 others of primary liver cancer.
- Cirrhosis and primary cancer of the liver are the terminal stages of numerous hepatic pathologies, such as viral hepatitis, alcoholic steatohepatitis and non-alcoholic steatohepatitis.
- Fatty liver disease of non-alcoholic origin is increasing rapidly, together with the Western obesogenic way of life, Type 2 diabetes, hyperlipidaemia, hypertension and metabolic syndrome.
- Childhood and young-adulthood obesity in particular are important risk factors for later cirrhosis and cancer of the liver.
- In Belgium the present rate of obesity is 15%. But in 2050, if nothing changes, the world will have 4 billion overweight or obese individuals, i.e. 60% of the population. Of these 4 billion, 20% to 25% will develop a fatty liver and 5% will go on to have NASH.

BIOBANKS: ESSENTIAL FOR RESEARCH ON NASH

The term biobank refers to a structured collection of human biological samples (tissues, blood, urine etc.) and associated data (health parameters, history of the disease and treatment, life- style etc.), stored for the purposes of present and future research.

For their research on fatty liver and NASH, clinicians and researchers require liver tissues and blood, urine and stool samples from patients and from healthy persons, as well as other elements gathered by the biobanks. What is under discussion here is clinical biobanks, focused on disease and, more specifically, liver disease: liver-tissue biobanks. How should they be developed and used most effectively to optimise their contribution to research aimed at better prevention and treatment of NASH? Thanks to the NASH & BIOBANKS project, liver specialists and managers of biobanks have been able to discuss these issues not only among themselves but also with patients and the general public.

"In healthcare we are at present facing major challenges. Challenges involving in particular faster and more efficient and also more conscientious ways of translating new ideas and scientific discoveries into medical applications capable of having a decisive impact on patients and society. Although this topic has to be to dealt with at different levels, it also concerns the development of instruments for collecting and sharing data and research material, now and in the future. Here automatically we must think of biobanks and biobank networks. If biobanks succeed in organising themselves in a pre-competitive and common infrastructure, centred on the wellbeing of all, they will be of inestimable value for biomedical research and its effects on the improvement of health, prevention, diagnosis and the treatment of diseases."

Prof. Sofie Bekaert, chairwoman BBMRI.be

Chapter 2.

From initial exchanges to future questions: one year of dialogue

How did we reach a research agenda?

Involving the right people and exploring the field

23 March 2017
Exploratory workshop

Putting the right focus on the project

30 June 2017
Focus and scope meeting

Liver disease
x biobanks
→
Criteria to determine a focus (determined by citizens, patients, hepatologists and biobank managers)
→
NASH x biobank

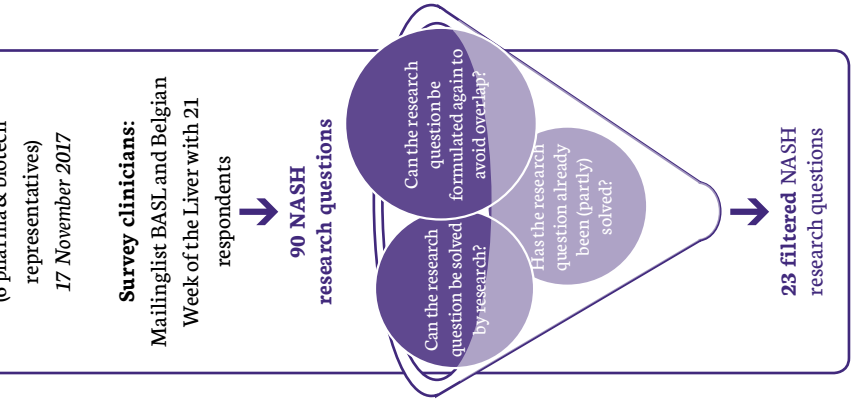
Harvest the right topics for research questions

Focus group biobank managers (15)
4 October 2017

Focus group citizens and patients (14)
14 November 2017

Focus group industry
(6 pharma & biotech representatives)
17 November 2017

Survey clinicians:
Mailinglist BASL and Belgian Week of the Liver with 21 respondents
→
90 NASH research questions



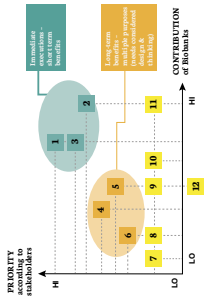
→
23 filtered NASH research questions

Seeking consensus and prioritisation

12 January 2018
Steering committee selects from the 23 NASH questions the questions with a possible contribution of biobanks

2 februari 2018
Consensus meeting with all the involved stakeholders

PRIORITISATION of research questions



25 May 2018
Feedback from ethics experts

Reporting and dissemination

Reporting and publication:
3 pilot projects and methodology for priority-setting

PUTTING THE RIGHT FOCUS ON THE PROJECT

During a first meeting for discussion and raising of awareness, on 30 June 2017, citizens, patients, clinicians, researchers, biobank managers and healthcare professionals exchanged information and preoccupations regarding the challenges arising from liver disease in general and discussed the establishment of a common basis for research topics, the possible role of biobanks and the ethical, legal, social and governance aspects pertaining to biobanks. They developed a series of criteria, after which the steering committee finally defined the direction and scope of the project: 'NASH and the contribution of biobanks'.

HARVEST THE RIGHT TOPICS FOR RESEARCH QUESTIONS

1. Carrying out a survey among hepatologists, gastroenterologists and hepatology researchers.

2. Organising group discussions:

- 4 October 2017: Focus group with 15 biobank managers.
- 17 November 2017: Focus group with 14 citizens and patients.
- 17 November 2017: Focus group with 6 representatives of the pharmaceutical and biotechnology industry.

Each time these discussions were opened by a presentation on NASH or biobanks or both, depending on the parties involved. All elements for debate identified during these discussions were grouped by topic and questions were extracted from each topic or sub- topic. For NASH, this stage produced 90 questions.

3. Filtering the questions:

- The question has already had an answer through scientific research
- The question does not need scientific research
- Duplication or possibility of grouping together

Following implementation of these various filters and after verification and reformulation, these 90 questions were reduced to 23.

SEEKING CONSENSUS AND PRIORISATION

On 12 January 2018, these 23 questions were submitted to a steering committee consisting of two hepatologists and three biobank managers. For each question, the members of the committee considered to what extent the biobanks could contribute to the research question. After mature reflexion, they identified 14 questions.

Finally, on 2 February 2018, a dialogue day, which brought together a varied group of people combining lay people, patients, clinicians, researchers, biobank managers and healthcare professionals, focused on these 14 NASH questions, as well as on a series of 28 questions concerning biobanks, divided into two large categories: 18 questions on general biobank problems and 10 questions specifically dealing with biobanks in their relationship with NASH.

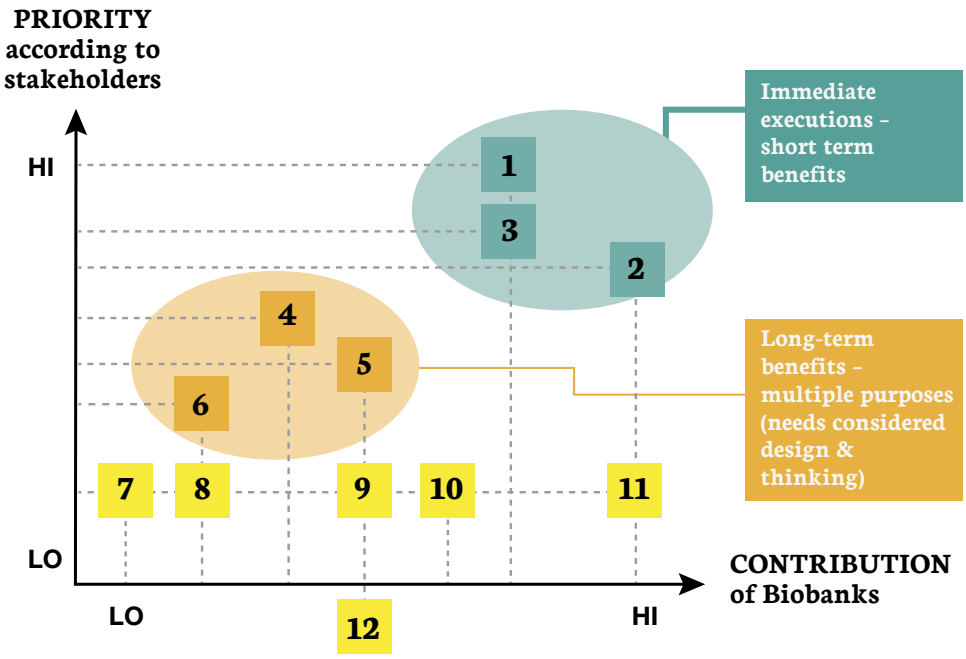
> *"With regard to NASH, we often have difficulties seeing the realities with which we are confronted. To improve care we must broaden our view. Are patients ready for this exercise? I'm convinced they are, provided they are properly informed. Is the industry ready for this exercise? And the medical staff? I am afraid that in this case, the dialogue with other stakeholders, for example patients, remains to be established. Regarding the lawmakers and ethics experts, the question remains open."*
>
> Professor Hans Van Vlierberghe, Gastroenterologist, UZ Gent

Chapter 3. The priority questions concerning fatty liver and NASH

The committee members first of all prioritised the 14 questions identified on the basis of the possible biobank contribution involved (X axis of the figure below). The more a question is located to the right, the greater the possibility of a biobank contribution.

Following this, the participants in the Dialogue Day reduced the 14 questions to 12 using a combination system. They then assigned a level of societal importance to each question (Y axis) starting from the premise that they were all important, but some more so than others. The higher the location of the question on the Y axis, the more the participants consider it socially important.

This 'two-dimensional prioritisation' produced the figure below.



Twelve priority research questions	
N1	*Which pathophysiological mechanisms are involved in fatty liver and NASH? How can the liver cells be protected against an accumulation of lipids and the subsequent development of NASH, cirrhosis and liver cancer?*
N2	*Why, with the same life-style, do some people develop NASH and others don't? Which genetic factors contribute to a fatty liver and NASH?*
N3	*Which non-invasive methods (biomarkers, imaging etc.) could improve the diagnosis of NASH, help in determining the stage of the disease and in detecting which patients are most at risk of progression of the disease, and make follow-up treatment more effective?*
N4	*What is the epidemiology of fatty liver or NASH, in Belgium, in the general population? What is the true prevalence of the disease and the speed of passing from one phase to the other? Which cohorts of the population are most at risk?*
N5	*What is the role of processed foods (e.g. sweet drinks, certain fats etc.) and the food industry in the onset of fatty liver and NASH?*
N6	*How can NASH be treated 'intelligently', in order to optimise the health and quality of life of the patient in general, now and in the future, taking into account the comorbidities of NASH? In other words, how can NASH be approached as a multi-organ disease rather than a liver disease?*
N7	*When does the disease become irreversible?*
N8	*What is the impact of a fatty liver and NASH on other organs? Which comorbidities are linked to fatty liver and NASH?*
N9	*Which life-style factors lead to fatty liver and to NASH? Specifically, which life-style poses a risk of NASH?*
N10	*What contributes most to a fatty liver and NASH: nature or nurture? Which interactions between natural disposition and behaviour lead to NASH?*
N11	*How does the microbiota (intestinal flora) contribute to fatty liver and NASH?*
N12	*Which socioeconomic factors contribute to fatty liver and NASH?*

The first group, on the upper right of the diagram, brings together three high-priority questions concerning fundamental research for which biobanks, in their present form, could make all the difference.

The second group, at the centre of the diagram, contains three systemic questions, for which biobanks may some day make a difference provided that their design develops.

The third group, consists of six more targeted questions, whose relevance to biobanks is highly variable.

> *"When I was asked to take part in this project as citizen, I felt obliged to accept. Not only because there are so many cancers in my family and that anything that might help to protect my children from this disease was something I wanted to do. I had also never heard of biobanks and wanted to know more about them. But above all because, for the first time in my life, I was asked to give my opinion as a member of the public and to become involved in a discussion which did not only concern me personally, but in some way, the whole population of Belgium and even of the world. This is the fourth time I have taken part and each time, at the end of the day, I was glad that I was there, because I have been listened to and my arguments have been passed on to people that I have never met but who continue the reflection process."*
>
> Mario Breugelmans, citizen

THREE QUESTIONS FOR WHICH BIOBANKS, IN THEIR PRESENT FORM, COULD MAKE ALL THE DIFFERENCE

According to the stakeholders, the priority of these research questions could be considered to be high, both regarding the knowledge and treatment of NASH and the contribution of the biobanks. In addition they can be activated almost at once, ensuring short-term benefits.

N1	*Which pathophysiological mechanisms are involved in fatty liver and NASH? How can the liver cells be protected against an accumulation of lipids and the subsequent development of NASH, cirrhosis and liver cancer?*
N2	*Why, with the same life-style, do some people develop NASH and others don't? Which genetic factors contribute to a fatty liver and NASH?*

For citizens and patients as well as for hepatologists, there can be no doubt: these questions are inextricably linked, because they aim at understanding the mechanisms responsible for the present epidemic of fatty liver and NASH. "To act, we must first understand" a hepatologist sums up. "An inexplicable problem can't be solved!"

From this point of view the most important question, according to all the stakeholders, is definitely No. 2: "*Why, with the same life-style, do some people develop NASH and others don't? Which genetic factors contribute to a fatty liver and NASH?*" At one of the tables, a citizen recognised to his astonishment that his life-style and particularly his diet – cakes, sweet things, crisps, alcohol, hamburgers and chips – ought to cause him enormous problems, while he was in perfect health. Why, out of two people leading the same notoriously unhealthy life, does one develop the disease and the other does not?

This situation is a matter of concern for hepatologists, who say that they are unable to predict how an individual person will develop. For patients and citizens this is difficult to accept. All the more so as each preventative measure that they suggest is immediately invalidated by the "Yes, but ..." of the specialists. The idea of initiating not only an awareness campaign but also screening from primary school with the help of PMS [Psycho-Medico-Social] centres, for example, comes up against legal constraints. "Because the risk factors have not been clearly identified and tests to detect them have not been developed, we cannot tell the school doctor what he/she must look for," explains a hepatologist. "We do not 'know' whether this or that child is at risk, we only suppose this. For example, every obese child will not develop liver disease. Out of 100, maybe 10 will be affected. The others will remain in good health for a long time. We suspect certain mechanisms but these have not been clearly documented. NASH is a complex disease which requires that we explore several paths at the same time in order to understand the stages, and then, following this, develop the approaches making it possible to intervene in these stages." Research to which biobanks can obviously contribute.

N3 *Which non-invasive methods (biomarkers, imaging etc.) could improve the diagnosis of NASH, help in determining the stage of the disease and in detecting which patients are most at risk of progression of the disease, and make follow-up treatment more effective?*

The importance of this question is evident, both for research and for treatment of the patient. At present it is impossible to diagnose NASH without carrying out a liver biopsy. This biopsy involves certain risks, particularly serious haemorrhage – rare (one in 5000) but which can lead to death. Having simpler and less invasive methods than biopsies would facilitate detection, treatment and treatment follow-up. According to a participating General Practitioner, this would allow GPs to play a more active role in the diagnosis and treatment of NASH.

THREE QUESTIONS FOR WHICH BIOBANKS CAN MAKE A DIFFERENCE IN THE LONG-TERM DEPENDING ON THEIR DEVELOPMENT

According to the stakeholders, these questions are of medium priority, both for knowledge and treatment of NASH and the contribution of biobanks.

N4 *What is the epidemiology of fatty liver or NASH, in Belgium, in the general population? What is the true prevalence of the disease and the speed of passing from one phase to the other? Which cohorts of the population are most at risk?*

For various reasons – a lack of global strategy for longitudinal health-data information, need for an independent body to coordinate these data, insufficient data gathering, lack of synergy at Federal, Community and Regional levels etc. - Belgium is known to be lacking in quality epidemiological studies. Fortunately the necessary information is already available at the European level. As emphasised by a hepatologist, "the European map of the prevalence of NASH is, to be sure, based on approximations, but from these data (however relative they may be) we can get a rough idea of the problem in Belgium. Certainly more precise data could only be of benefit to healthcare policy in Belgium, but the figures at our disposal (margin of error taken into account) are sufficiently reliable to serve as a basis. To have purely Belgian data would require a considerable effort, and this would have to be looked at in a cost-benefit context".

N5 *What is the role of processed foods (e.g. sweet drinks, certain fats etc.) and the food industry in the onset of fatty liver and NASH?*

This question divided the participants: some thought that investing in this research would make it possible to expose the responsibility of the industry, others claiming that diet is above all a question of life-style and therefore an individual choice.

"Most of the answers are already known," insisted a hepatologist. "Too much sugar, too much fat is dangerous, we all know that. But if the public does not change its behaviour, the food industry won't change. It will content itself with publicity stunts, as it has done recently: 'We have already reduced the sugar levels in our products by 5%!' But 95% instead of 100%, where does that get us? With regard to this, all the research in the world will do nothing if consumers do not systematically boycott processed foods. No point in targeting specific groups: to make the industry change its production methods radically there must be a general mobilisation of the population, a global life-style change. There are other factors which could be tackled more rapidly and effectively for the good of the patient!"

N6 *How can NASH be treated 'intelligently', in order to optimise the health and quality of life of the patient in general, now and in the future, taking into account the comorbidities of NASH? In other words, how can NASH be approached as a multi-organ disease rather than a liver disease?*

While this question may go over the heads of citizens and patients, for doctors, wishing to improve care, it has a definite interest. As for the experts, they are limited, here as elsewhere, by all that they do not know – or do not know yet – about NASH. As one hepatologist commented, in certain patients fatty liver disappears if there are changes in health habits, while in others, the same measures, and even more radical ones, produce no effect at all. Why? And in addition, how can we know whether NASH was already present when another disease, affecting a different organ, began to show? Is an overweight person with NASH at greater risk of developing cancer, for example, than an overweight person without NASH, or than someone with NASH but of normal weight (this also exists). As long as these why and how questions remain unanswered it will be difficult to deal with NASH in an "intelligent" way.

SIX SPECIFIC QUESTIONS …

… to which the stakeholders accorded a lower priority in the context of NASH, while being divided regarding the contribution of the biobanks.

N7 *When does the disease become irreversible?*

The patients themselves did not see the interest of this question, or rather preferred not to know the answer. The caregivers saw it more as a handicap than as a stimulus: once a disease has been labelled "irreversible", the compliance of the patient is often destroyed. As for the scientists, they obviously did not consider the question of irreversibility as without importance, but they saw it as only the logical continuation of a series of other questions: "When we know enough about the epidemiology of NASH (N3) to extract reliable markers (N4)", summed up an oncologist "the pathophysiological mechanisms involved in the disease (N1) will be clearer to us and we will be able to deduce if and when it becomes irreversible".

N8 *What is the impact of a fatty liver and NASH on other organs? Which comorbidities are linked to fatty liver and NASH?*

According to the doctors this question, which is inseparable from that of the possibility of treating NASH in an "intelligent" way in the context of a multi-organ disease (N6), is often put the other way round: what is the impact of comorbidities on the onset of fatty liver? To be sure, we are beginning to ask ourselves if a fatty liver is not a cardiovascular risk factor and if people with a fatty liver are not at greater risk of an infarction or thrombosis. But generally a fatty liver is seen as a complication rather than a triggering factor. An oncologist pointed out, however, that in many patients with cancer (of whatever kind), a liver ultrasound examination shows a fatty liver, even NASH. Should it be concluded that a fatty liver and NASH are related to all cancers, and not just liver cancer? In the present state of our knowledge, this question must remain open.

N9 *Which life-style factors lead to fatty liver and to NASH? Specifically, which life-style poses a risk of NASH?*

This question is obviously not without interest with regard both to prevention and treatment, but the citizens and patients as well as the doctors and specialists all agreed that the life-style factors are already very well – too well? – known. "Don't drink, don't eat this, don't do that …." a patient mocked. "Doctors always harp on about the same things, but that doesn't answer our main question: why has this happened to me when I know a heap of people whose life-style is worse than mine and who have no problem?" - adding that the actions taken to encourage a healthier way of life can do more harm than good.

For one doctor the problem is not any ignorance of what constitutes an anti-NASH life-style. "Today nearly everybody knows perfectly well what a healthy life-style is," she said. "But knowing and understanding are not the same thing. Plenty of people quite simply refuse to admit that they are directly concerned by the advice regarding life-style. They prefer to talk about hereditary problems because, that way, they can avoid having to take their health into their own hands."

N10 *What contributes most to a fatty liver and NASH: nature or nurture? Which interactions between natural disposition and behaviour lead to NASH?*

According to the participants, the impact of this question is limited, both for research and for patients and the general population. The also considered that it duplicated the questions concerning the reasons for the development or non-development of NASH in people apparently with the same life-style (N2) and concerning the pathophysiological mechanisms involved in the development of the disease (N1).

N11 *How does the microbiota (intestinal flora) contribute to fatty liver and NASH?*

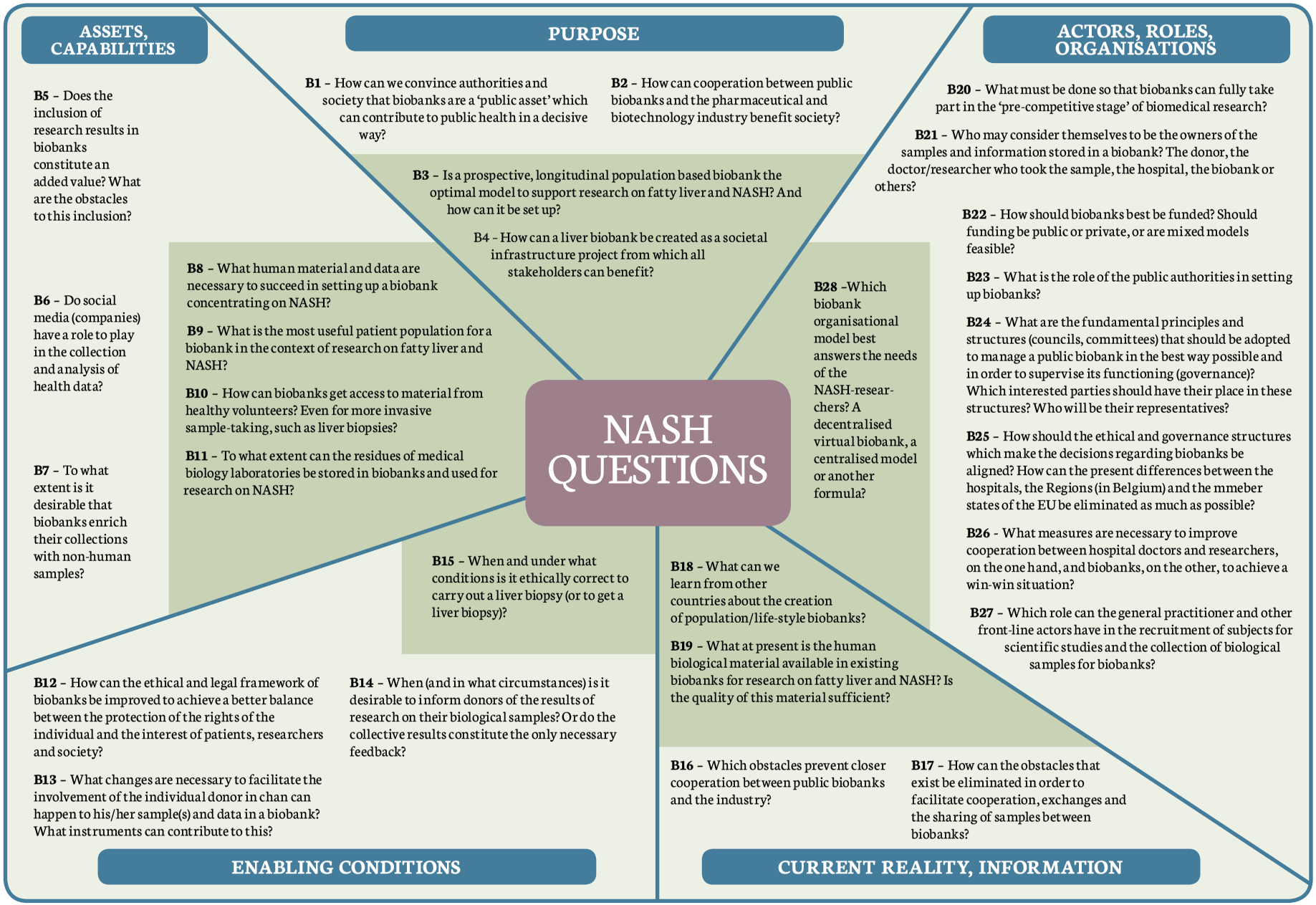
During the discussions opinions were very divided, but the opinion of some of the hepatologists present prevailed. According to them, microbiota is so "fashionable" and is the subject of so much research that it would be pointless to focus on it in the context of a campaign against NASH. One hepatologist regretted this sidelining of the question, of a specific kind to be sure but nonetheless important and in the resolving of which biobanks could play a vital role.

According to the participants this question runs the risk of stigmatising people, without any benefit either to the population or research. One oncologist, however,

N12 *Which socioeconomic factors contribute to fatty liver and NASH?*

pointed out that socioeconomic factors cannot be ignored in the fight against cancer in general, the survival rate among people affected being notoriously lower in the underprivileged social classes. However, as a patient emphasised, you can be socioeconomically privileged and have an extremely unhealthy life-style and, particularly, diet!

Chapter 4. The role of biobanks in all of this?


ASSETS, CAPABILITIES
PURPOSE
ACTORS, ROLES, ORGANISATIONS
NASH QUESTIONS
ENABLING CONDITIONS
CURRENT REALITY, INFORMATION
B1 – How can we convince authorities and society that biobanks are a 'public asset' which can contribute to public health in a decisive way?
B2 – How can cooperation between public biobanks and the pharmaceutical and biotechnology industry benefit society?
B3 – Is a prospective, longitudinal population based biobank the optimal model to support research on fatty liver and NASH? And how can it be set up?
B4 – How can a liver biobank be created as a societal infrastructure project from which all stakeholders can benefit?
B5 – Does the inclusion of research results in biobanks constitute an added value? What are the obstacles to this inclusion?
B6 – Do social media (companies) have a role to play in the collection and analysis of health data?
B7 – To what extent is it desirable that biobanks enrich their collections with non-human samples?
B8 – What human material and data are necessary to succeed in setting up a biobank concentrating on NASH?
B9 – What is the most useful patient population for a biobank in the context of research on fatty liver and NASH?
B10 – How can biobanks get access to material from healthy volunteers? Even for more invasive sample-taking, such as liver biopsies?
B11 – To what extent can the residues of medical biology laboratories be stored in biobanks and used for research on NASH?
B12 – How can the ethical and legal framework of biobanks be improved to achieve a better balance between the protection of the rights of the individual and the interest of patients, researchers and society?
B13 – What changes are necessary to facilitate the involvement of the individual donor in chan can happen to his/her sample(s) and data in a biobank? What instruments can contribute to this?
B14 – When (and in what circumstances) is it desirable to inform donors of the results of research on their biological samples? Or do the collective results constitute the only necessary feedback?
B15 – When and under what conditions is it ethically correct to carry out a liver biopsy (or to get a liver biopsy)?
B16 – Which obstacles prevent closer cooperation between public biobanks and the industry?
B17 – How can the obstacles that exist be eliminated in order to facilitate cooperation, exchanges and the sharing of samples between biobanks?
B18 – What can we learn from other countries about the creation of population/life-style biobanks?
B19 – What at present is the human biological material available in existing biobanks for research on fatty liver and NASH? Is the quality of this material sufficient?
B20 – What must be done so that biobanks can fully take part in the 'pre-competitive stage' of biomedical research?
B21 – Who may consider themselves to be the owners of the samples and information stored in a biobank? The donor, the doctor/researcher who took the sample, the hospital, the biobank or others?
B22 – How should biobanks best be funded? Should funding be public or private, or are mixed models feasible?
B23 – What is the role of the public authorities in setting up biobanks?
B24 – What are the fundamental principles and structures (councils, committees) that should be adopted to manage a public biobank in the best way possible and in order to supervise its functioning (governance)? Which interested parties should have their place in these structures? Who will be their representatives?
B25 – How should the ethical and governance structures which make the decisions regarding biobanks be aligned? How can the present differences between the hospitals, the Regions (in Belgium) and the mmeber states of the EU be eliminated as much as possible?
B26 - What measures are necessary to improve cooperation between hospital doctors and researchers, on the one hand, and biobanks, on the other, to achieve a win-win situation?
B27 – Which role can the general practitioner and other front-line actors have in the recruitment of subjects for scientific studies and the collection of biological samples for biobanks?
B28 –Which biobank organisational model best answers the needs of the NASH-researchers? A decentralised virtual biobank, a centralised model or another formula?

In order to mobilise them appropriately, we must get to know them better. Through a procedure comparable to that used for NASH, the elements concerning biobanks were brought together in 28 questions, which were divided into two large categories: on the one hand, 10 questions concerning the challenges faced by biobanks in relation to NASH, on the other hand, 18 questions on the general problems of biobanks.

BIOBANKS IN 28 QUESTIONS

These questions were separated into different categories:

- **Purpose:** from the point of view of society, what should a biobank contribute to? And, more specifically, a liver biobank?
- **Assets and capabilities:** biobanks, what must they be able to do?
- **Enabling conditions:** in what legal, ethical and financial framework should biobanks operate?
- **Current reality, information:** what is the situation today? In Belgium, but also, where relevant, in other countries?
- **Actors, roles, organisations:** who is involved in this process?

These questions were submitted to the participants on the dialogue day, in the form of the diagram above. The questions concerning biobanks in their relationship with NASH are dealt with in the darker inside circle and the general questions on biobanks in the lighter outside circle. The participants were asked to go through these questions, to consider what major issues they pose for society and to suggest, if possible, any solutions. Discussion developed quite naturally in the framework of the categories summarised above.

"We realised that there was a lot of 'residual' material that had been taken for pathology diagnostics which was stored in our archives and remained unused. Some of it was just thrown into the bin. However, Belgium uses the "no-objection" system: if the patient does not formally object to his/her biological material being used for research, it can be made available to researchers. But to do this, storage and in particular the identification of this human biological material must be improved so that researchers can get what they need. This is how our biobank was born. It then became part of a network of biobanks, so that researchers could be informed about what we are making available to them. But we very quickly understood that just facilitating the transfer of existing material to researchers in good administrative and ethical conditions was not sufficient. They often needed additional material – blood samples etc. – which we had not thought of. So the third purpose of biobanks, after storage and transfer of human biological material, is to be an intermediary between researchers, who have questions and need the material to answer them, and clinicians who can provide them with this material."

Étienne Marbaix, Biothèque UCL

Purpose

BIOBANKS IN GENERAL

B1

How can we convince authorities and society that biobanks are a "public asset" which can contribute to public health in a decisive way?

In the past authorities had a tendency to consider biobanks as potential gold mines, the human "ore" of which could be sold to the pharmaceutical or biotechnology industry, or even to leading international players in the area of research. However, so that biobanks can be of benefit to all, it is of capital importance to replace this model – the biobank as an economic asset –with another– the biobank as a public asset, situated in the pre-competitive area of medical research – and to build it into a truly societal project and not one aimed only at enhancing the status of universities and university hospitals. This does not mean that in the long term biobanks will not contribute to enriching society, provided one accepts that the return on investment is not counted only in hard cash but also in new scientific, medical and clinical prospects, more precise diagnostics, more effective therapies, a better quality of life for patients and better health for everybody!

B2

How can cooperation between public biobanks and the pharmaceutical and biotechnology industry benefit society?

While the managers of biobanks consider biotechnology companies as 'natural' partners, their cooperation with pharmaceutical companies appears less balanced, even ambivalent. However, society has need for both one and the other in order to develop new biomarkers, diagnostic tests, medications and treatments - all developments for which biobanks are an essential tool. This is why the national and international authorities should actively support cooperation between the biobanks and industry by developing a specific legal and regulatory framework.

NASH BIOBANKS

B3

Is a prospective, longitudinal population based biobank the optimal model to support research on fatty liver and NASH? And how can it be set up?

One thing is certain, the creation of a prospective, longitudinal biobank, based initially on a target population in good health or one at risk of NASH but without manifest disease is beyond the capability of existing biobanks, which collect the greater part of their samples through the hospitals. Apart from this, almost all university

hospitals have their own biobanks. It is obviously impossible to create control groups without having biological material coming from persons in good health. To overcome this problem, Belgian biobanks should develop new strategies in order to obtain 'non-patient' samples from people who, by definition, do not frequent hospitals. But Belgian legislation, as it stands, does not facilitate the task.

B4 *How can a liver biobank be created as a societal infrastructure project from which all stakeholders can benefit?*

In this particular case, what we need is a co-creation model producing an infrastructure which is useful to all parties involved: doctors and researchers, pharmaceutical and biotechnological industry, funders and governments, but also patients and members of the public. This would require the European and Belgian (Federal and Regional) authorities to draw up consistent and synchronised legislation.

Assets and capabilities

BIOBANKS IN GENERAL

B5 *Does the inclusion of research results in biobanks constitute an added value? What are the obstacles to this inclusion?*

When a sample has been included in a study, the results of the experiments carried out on it can be entered into the database of the biobank. The advantage of this is that it can prevent repetition of the same experiments on the same samples. However, this is often not done because of the huge problems that it poses for the organisation, computer support systems etc.

B6 *Do social media (companies) have a role to play in the collection and analysis of health data?*

Among the healthy volunteers and patients possibly interested in giving their data and body samples to a biobank for research purposes, many exchange their views regarding life-style on Facebook and other social media. All these data could contribute to the success of the project, provided that their use has been approved ethically and the regulations for the protection of privacy are complied with. The social media could also be a fast and easy way of communicating with potential donors and of establishing a real social network around a biobank project.

B7 *To what extent is it desirable that biobanks enrich their collections with non-human samples?*

At present biobanks concentrate on human material only, although the need for animal material is considerable. Biobanks could therefore usefully extend their range of action. Not that they should be expected to take the place of breeding farms but there is nothing to stop them from storing/archiving the animal material left over by some researchers.

NASH BIOBANKS

B8 *What human material and data are necessary to succeed in setting up a biobank concentrating on NASH?*

This is a particularly difficult question, as the range of the end users' possible research interests is vast. How can one prioritise the material and data to be collected if the research themes themselves have not yet been defined? The creation of a really useful biobank therefore requires, above all, discussion with the end users, in order to anticipate future needs.

B9 *What is the most useful patient population for a biobank in the context of research on fatty liver and NASH?*

One of the problems with present biobanks is that most of their samples come from patients at an advanced stage of the disease. To be effective, a NASH biobank must contain samples taken at the earliest stages of the disease, as well as biological samples from healthy donors.

B10 *How can biobanks get access to material from healthy volunteers? Even for more invasive sample-taking, such as liver biopsies?*

As people in good health, whose biological samples are essential for the creation of control groups, do not frequent hospitals, biobanks would be well advised to cooperate with general practitioners, who could serve as intermediaries between them and the donors. An adaptation of the law is however desirable: at present a person in good health is not authorised to donate body samples through liver biopsy, even if he/she is completely informed of the risks and simply wishes to invest in a future where he/she or a member of his/her family could benefit from the progress made thanks to the donation.

B11 *To what extent can the residues of medical biology laboratories be stored in biobanks and used for research on NASH?*

Body samples remaining after diagnostic tests or surgery may be stored and used for scientific research together with certain related data. But should it be anonymised, or coded with a view to further investigations? In any case the present informed consent procedure needs to be relaxed.

Enabling conditions

BIOBANKS IN GENERAL

B12 *How can the ethical and legal framework of biobanks be improved to achieve a better balance between the protection of the rights of the individual and the interest of patients, researchers and society?*

Patients and members of the public, whom ethics committees try to protect in an absolute way, indicate for their part a wish to participate. Clearly, it is important that ethics committees oversee the safe use of this material and that the privacy and confidentiality of the donor be monitored. However, the committees seem to want to protect these rights in an absolute way and the current legislation makes it almost impossible for patients and citizens to participate (on their own initiative) in research.

Another problem: any discovery, even a tiny one, must systematically be reported to the donor. Ethics Committees see in this an additional reason to block the collecting of body samples from healthy donors, unless the samples are totally anonymised, which makes them much less useful for research.

Conclusion: it would be wise to balance the regulations and practises involved, taking more account of the interests of society – as the end user of the results of research and of the new medical developments arising from them.

B13 *What changes are necessary to facilitate the involvement of the individual donor in what can happen to his/her sample(s) and data in a biobank? What instruments can contribute to this?*

It is obviously essential to make donors understand how donation is interesting for them. But is it necessary all the same to give them the right to decide if, how and when their samples may be shared between different research projects, or is it enough to explain the importance of their contribution to society? The question merits consideration.

B14 *When (and in what circumstances) is it desirable to inform donors of the results of research on their biological samples? Or do the collective results constitute the only necessary feedback?*

Obviously certain tangible elements obtained from their biological samples must be passed on to the donors. But it is not absolutely necessary that these elements be closely related to their own health. Experience shows that, for them, something that is good for society in general, for healthcare or for science is just as rewarding, even more so.

> *"At present the lawmaker concentrates above all on the rights of the patient. Patients have the right to be informed if research using their samples produces interesting data about their health. Due to the present wording of the legislation, traceability is so advanced that in practice it has become very difficult for researchers systematically to ensure the traceability of what they have taken from a sample. This constitutes an obstacle for research. The conflict between the interests of the individual and those of society in the area of proper and effective research results in excessive demands being placed on research. We must immediately find a balance here, so that the interests of one are not detrimental to the interests of the other."*
>
> Dr René Custers, Regulatory & Responsible Research Manager, VIB

> *"The challenges related to biobanks are not new. These subjects have already been widely discussed by many. And we have seen plenty of tendencies in different directions. These topics are obviously an integral part of a changing society. The question is whether we will ever achieve a lasting and sufficiently broad answer to satisfy everybody."*
>
> Professor Pascal Borry, bioethics specialist at the Interfacultair Centrum voor Biomedische Ethiek en Recht, KU Leuven

NASH BIOBANKS

B15 *When and under what conditions is it ethically correct to carry out a liver biopsy (or get a liver biopsy)?*

As has been said above, this biopsy is not risk-free. For sick donors the problem does not exist, the biopsy being necessary for the diagnosis. But to impose it on healthy donors just for the purpose of constituting control groups is considered unacceptable within the European health system, even if potential donors are informed and consenting. In this debate, however, the only people who are never consulted are precisely these healthy members of the public, of whom some are ready to undergo this procedure, arguing that, some time in the future they or members of their families could benefit from the research. Once again, allowing ALL the parties involved to have their say would be a first step in the right direction.

Current reality, information

BIOBANKS IN GENERAL

B16 *Which obstacles prevent closer cooperation between public biobanks and the industry?*

According to the managers of biobank managers, 3 elements are involved:

1. Big Pharma is only interested in the samples, not in cooperation;
2. With the huge budgets available to it, it only reckons in terms of return on investment;
3. Pharmaceutical companies have their own biobanks which are not open to the public.

As mentioned above, the relationship between public biobanks and pharmaceutical companies is ambiguous. A balanced dialogue on the possibilities of collaboration is desirable.

B17 *How can the obstacles that exist be eliminated in order to facilitate cooperation, exchanges and the sharing of samples between biobanks?*

This cooperation is essential: numerous studies require such a quantity of samples that one single biobank is not enough. Harmonised operation of biobanks and the installation of a 'free access' system would facilitate exchanges between them, not to mention the day-to-day lives of researchers!

NASH BIOBANKS

B18 *What can we learn from other countries about the creation of population/life-style biobanks?*

The problems Belgian biobanks face, are found also in other European countries: lack of funds, lack of long-term vision, ethical and legal issues. However, progress has been made at the international level during the last five years, particularly with the MIABIS (Minimum Information About Biobank Data Sharing) model, representing the minimum information necessary to commence cooperation between biobanks and facilitate the exchange of samples and data. But the ideal would be to emulate the Swiss model, where tools (e.g. applications) make it possible to ask the patient/donor regarding all the possible uses of his/her samples.

B19 *What at present is the human biological material available in existing biobanks for research on fatty liver and NASH? Is the quality of this material sufficient?*

To answer this question, one would have to start by drawing up an inventory of everything that is already available in existing biobanks and of what must still be collected. The quality would also have to be checked, the older material having been collected at a time when the requirements in this area were not as great as they are now and the storage conditions sometimes bad.

> *"The various workshops of this project were a real revelation for me. I was obliged to step outside my usual environment. I discovered perspectives I had never thought about before. Dialogue of this type with all the stakeholders would have been invaluable when the Vlaams Biobank Netwerk was being launched."*
>
> Professor Sofie Bekaert, chairwoman BBMRI.be

Actors, roles, organisations

BIOBANKS IN GENERAL

B20 *What must be done so that biobanks can fully take part in the 'pre-competitive stage' of biomedical research?*

The end users (researchers and clinicians) must be brought together and a part of the available budget must be used to encourage cooperation, the collection of samples (funds have been proposed to clinicians to encourage the nursing staff and other healthcare staff in the collection of biological material) and to create connections between biobanks. According to some participants in the dialogue day, this support given to research projects at the pre-competitive stage is of the very essence of biobanks.

B21 *Who may consider themselves to be the owners of the samples and information stored in a biobank? The donor, the doctor/researcher who took the sample, the hospital, the biobank or others?*

At present the situation varies considerably from one biobank to another. But we must not lose sight of the fact that the samples should be considered as a 'common asset' of society.

B22 *How should biobanks best be funded? Should funding be public or private, or are mixed models feasible?*

Some companies have their own biobanks, entirely financed and managed by themselves. Others cooperate with public or private biobanks, to the funding of which they contribute, or with hospitals. A particularly efficient model is that of the Luxembourg biobank where all the samples are centralised in a single university biobank, attached to the University General Hospital of the Grand Duchy. But the Luxembourg government has invested no less than 40 million euro in it!

B23 *What is the role of the public authorities in setting up biobanks?*

As well as transposing European directives into local law, they invest in new technologies, among which biobanks. But in Belgium the various levels of authority complicate the development of biobanks.

B24 *What are the fundamental principles and structures (councils, committees) that should be adopted to manage a public biobank in the best way possible and in order to supervise its functioning (governance)? Which interested parties should have their place in these structures? Who will be their representatives?*

The discussions revealed certain tensions between biobanks and ethics committees. In the interest of all, however, dialogue should be encouraged between the stakeholders, and the representatives of patients and the public should be included in the committees.

B25 *How should the ethical and governance structures which make the decisions regarding biobanks be aligned? How can the present differences between the hospitals, the Regions (in Belgium) and the member states of the EU be eliminated as much as possible?*

The broad answers are greater flexibility in the governance system, a better balance between the rights of researchers and those of patients and donors, and greater consideration for the choices of the general public.

B26 *What measures are necessary to improve cooperation between hospital doctors and researchers, on the one hand, and biobanks, on the other, to achieve a win-win situation?*

Most importantly there must be a better understanding between researchers and clinicians, on the one hand, and biobanks on the other. Certain researchers and clinicians still see biobanks as a necessary evil, instead of considering them to be valuable collaborators and co-creators of research programmes. The real value of biobanks must be better understood by these end users.

B27 *Which role can the general practitioner and other front-line actors have in the recruitment of subjects for scientific studies and the collection of biological samples for biobanks?*

The role of the general practitioner appears to be crucial in the recruitment of healthy donors.

NASH BIOBANKS

B28 *Which biobank organisational model best answers the needs of the NASH researchers? A decentralised virtual biobank, a centralised biobank or another formula?*

The models chosen in Belgium – by both Federal and Regional authorities – are based on decentralised biobanks. There are 3 biobank networks in Belgium created at the initiative of the levels of authority (Federal, Regional etc.). Although their activities overlap to some extent, they continue to have a certain degree of competition, while at the same time cooperating, as we have emphasized above, in the pre-competitive area. Some form of decentralisation would however be necessary, at least for 'minimal data'. In practice when a company needs samples, it can only get them by individual cooperation with a biobank.

IN SHORT: 10 CHALLENGES FOR THE BIOBANKS OF TODAY... AND TOMORROW

1. (RE)THINK THE DESIGN OF BIOBANKS TO ADAPT THEM TO OUR AMBITIONS

On the admission of biobank managers themselves, the present problem of biobanks is that they were set up according to specific needs, without being based on any initial overall design. "As a general rule," explains the hepatologist, Peter Stärkel, "a biobank is created by a researcher for a target group. Therefore there are oncology biobanks specialised in cancer samples, designed exclusively for cancer research, sometimes even targeting specific types of cancer."

Possible solutions?

Proceeding in three stages:

1. Define a biobank concept which includes the idea of the common good and is sufficiently capable of development so that the structures of the biobank eventually adapt to the needs of society;
2. Draw up an inventory of what actually exists in the area of biobanks;
3. On this double basis, develop a societal biobank organisational model that allows for the best use of the resources.

> *"The problem is that everyone – lawyer, bioethics specialist, researcher, patient, biobank manager etc. - approaches the issue from their own point of view, thinking theirs is more important than all the other ones. However, it is essential to start from the idea that ALL the stakeholders are of equal importance and that, when we reach a consensus, it must be on the widest base possible. Hence the importance of continuing the multi-party dialogue on the long-term."*
>
> Professor Peter Stärkel, hepatologist, UCL Saint-Luc

2. ESTABLISH A LEGAL AND ETHICAL FRAMEWORK FOR BIOBANKS

At present Belgium uses the no-objection system: the patient declares that he/she does not object to the use of his/her biological material for research. But for biological material taken in the framework of a specific project, this system does not apply. In other words, left-over samples may not be used by another researcher. Furthermore, when researchers need control elements coming from healthy donors, people in good health wishing to make a voluntary donation of their biological material are still prohibited from so doing.

"In what way does the sample taken from my liver and having pathogenic characteristics still continue to be me? In what way could the putting into circulation of this material be an infringement of my personal integrity? I don't think this goes without saying. Certainly it's not just the material that is circulated but also information which might be channelled for different purposes, such as for commercial profit, or, if it is given the status of a societal asset, simply for the benefit of society. And this is important for people. There are those who do not want their bodies to be changed into information, do not want the biological elements given by them to enable a profit to be made from something that cost nothing. But, for my part, I really have the impression that, if a biological element is taken from me, the important thing is less to know to what extent it is related to my person and what attacks it can have on me, but rather in what type of traffic it will enter: a sample can become waste that will be put in the trash, or else, and that's another thing, a stock of valuable information; an organ or tissue can be used as a material for science, or to repair someone else's life. My biological material is not me anymore. I would personally prefer that the trash where I threw away my biological material becomes a collective and free resource, where others might not see any objection to marketing. Anyway, I think that the question that matters, when it comes to biological material, is not primarily that of the protection of people (in terms of personal data for example) but the question of the modalities of the circulation and valuation of what, by being left aside, is somehow donated ... "

Florence Caeymaex, philosopher ULg, researcher FNRS, member of the Bioethics Consultative Committee of Belgium

"Perhaps in Ethics Committees it is not emphasized enough that the interest of the individual can also be the interest of the community. In our society which is extremely focused on the individual as a person, the idea of a donation to society is neglected too much. There is an urgent need for development in this area!"

Monique De Plaen, citizen

Possible solutions?

However important it may be to protect donors, the interests of researchers must not be neglected. The framework to be established must be clear, but not so restrictive as to hamper research. And it must take account (setting the necessary limits, of course) of the good will of people in good health who are ready to provide samples for comparison purposes.

3. HARMONISING LEGISLATION AT THE EUROPEAN LEVEL

This harmonisation is essential so that a researcher in Brussels, for example, can have access to a sample stored in a biobank in Marseille and use it for another purpose than that for which it was taken.

4. DRAWING UP OF FINANCIAL FORMULAS

Who will pay for what? The participants agreed on one point: the more independent the funding is, the better it is.

5. INVOLVE THE POLITICAL DECISION MAKERS

For the participants, politicians cannot stand back. Design of biobanks, funding, organisation: it is essential that they give their opinion. And voters should not hesitate to demand that election candidates take a clear position in this area.

> *"While the presence of members of the public is of interest and is productive, it should be asked who they represent – themselves, a group of individuals, a pressure group, and by virtue of what – and also how to connect up again with the elected representatives, because, without the elected representatives, there is no law. Legislative work is of great important in this regard."*
>
> Florence Caeymaex, philosopher ULg, researcher FNRS, member of the Bioethics Consultative Committee of Belgium

6. MAKING A BELGIAN BIOBANK NETWORK

Some Belgian biobanks are already in networks at the European level. Networks are essential to avoid waste and increase efficacy.

7. IMPROVE BIOBANK ACCESSIBILITY THROUGH THE INTERNET

The participants suggested creating a centralised virtual databank, allowing access through an interactive and comprehensible system and making it possible for any researcher to determine quickly and easily whether the biological material necessary to his/her research exists, where it is being kept and what the – legal and harmonised – conditions are for making it available.

Possible solutions?

The participants underlined the fact that the security element needs to be reviewed. As security systems continue to be upgraded, there comes a point when the systems are no longer able to communicate. Security must not be a constraint on connectivity. This technical problem requires a quick solution.

N.B.! Among the general public there is a certain apprehension at the idea of lifting the anonymity of samples. For longitudinal studies which require a certain repetitive process, anonymity is impossible: at some point it must be possible to identify the patient.

8. QUALITY CONTROL

The quality of the human material collected and the conditions in which it is kept must be as perfect as possible, which at the moment is not always the case.

Possible solutions?

Establish quality standards common to all biobanks and train supervisors who will be competent to verify their application.

9. SPREAD INFORMATION ON BIOBANKS

The participants were of the opinion that most of our fellow citizens know nothing whatsoever about biobanks. Proper information, not only for patients but for the public in general, is therefore necessary in order to increase the visibility of biobanks and to make the general public aware of the added value they represent both for the population as a whole and for patients and doctors.

Possible solutions?

Train biobank 'ambassadors' in order to raise public awareness and convey information.

Jumble of quotes

"A year ago I had never heard of biobanks. Now that I not only know what they are but the potential that they have for us all, I think it is imperative to inform the general public!" - "The missing link in this project is an association of NASH patients. There is nothing like associations for spreading information!" - "It should no longer be said to people who wish to donate their biological material, as they do money, that it is not possible. This must become possible." - "Because information is important, there must be more consistency in the answers given to patients!" - "The word 'biobank' is pejorative, because it contains the word 'bank'. Why not talk about 'biotrust', as did Professor Simon in Stockholm last year?"

"Researchers must make greater efforts to involve the public in their research. If we want the dialogue between researchers and the public to become real, we still have a lot to do!"

Professor Pascal Borry, bioethics expert at the Interfacultair Centrum voor Biomedische Ethiek en Recht, KU Leuven

10. TALK ABOUT THE SUCCESSES

"When successes are achieved thanks to the cooperation of a biobank, this should be announced immediately so that the public can understand the usefulness of biobanks", urged a participant, who underlined the snowball effect that could be obtained in this way. According to some participants, patients who have taken part in a successful research project through their biological samples should be informed and thanked.

CONCLUSION

Even if this project is only a first step, it succeeded in uniting around a table all the parties involved in the development of biobanks. Furthermore, it led to a real consensus regarding the importance of biobanks and the need to encourage the public to take part in this initiative.

These consultations with the stakeholders and the dialogue between them revealed numerous discrepancies between the expectations of the public/patients and the present context (legislative, regulatory, financial etc.) governing biobanks. A multi-party dialogue is therefore crucial, both between the various levels of authority and between the biobanks, researchers and clinicians, between public and private biobanks, between donors and biobanks etc. The importance of the involvement of all stakeholders, including patients/the public in the debate on the role and governance of biobanks, the regulations concerning them and the ethical aspects of their activities is all the more evident.

To sum up, the results of this project do not constitute a conclusion but an invitation to continue the dialogue about biobanks as a public asset contributing to public health and of course an urgent call for more sensitisation and more research on NASH.

> *"For me this project is not (yet) finished. This cannot be the final word. It must resume once more. NASH is already of considerable significance and it will gain in significance in the future. Similarly, nobody doubts the importance of biobanks for the development of research on NASH. This is why we must continue the dialogue. To overcome all the obstacles but also to encourage the decision makers to invest in these research issues."*
>
> Professor Hans Van Vlierberghe, gastroenterologist, UZ Gent

APPENDIX 1 – NASH & BIOBANKS QUESTIONS

The dialogue process for the NASH & BIOBANKS research generated 23 questions about NASH, of significant importance to the stakeholders involved. This appendix details the twelve questions in which biobanks have a role to play. It should be noted that originally questions N1 and N2 consisted of four separate questions.

N1	*Which pathophysiological mechanisms are involved in fatty liver and NASH? How can the liver cells be protected against an accumulation of lipids and the subsequent development of NASH, cirrhosis and liver cancer?*
N2	*Why, with the same life-style, do some people develop NASH and others don't? Which genetic factors contribute to a fatty liver and NASH?*
N3	*Which non-invasive methods (biomarkers, imaging etc.) could improve the diagnosis of NASH, help in determining the stage of the disease and in detecting which patients are most at risk of progression of the disease, and make follow-up treatment more effective?*
N4	*What is the epidemiology of fatty liver or NASH, in Belgium, in the general population? What is the true prevalence of the disease and the speed of passing from one phase to the other? Which cohorts of the population are most at risk?*
N5	*What is the role of processed foods (e.g. sweet drinks, certain fats etc.) and the food industry in the onset of fatty liver and NASH?*
N6	*How can NASH be treated 'intelligently', in order to optimise the health and quality of life of the patient in general, now and in the future, taking into account the comorbidities of NASH? In other words, how can NASH be approached as a multi-organ disease rather than a liver disease?*
N7	*When does the disease become irreversible?*
N8	*What is the impact of a fatty liver and NASH on other organs? Which comorbidities are linked to fatty liver and NASH?*
N9	*Which life-style factors lead to fatty liver and to NASH? Specifically, which life-style poses a risk of NASH?*
N10	*What contributes most to a fatty liver and NASH: nature or nurture? Which interactions between natural disposition and behaviour lead to NASH?*
N11	*How does the microbiota (intestinal flora) contribute to fatty liver and NASH?*
N12	*Which socioeconomic factors contribute to fatty liver and NASH?*

APPENDIX 2 – NASH QUESTIONS WITHOUT BIOBANKS

This annex details the nine NASH research questions, important for stakeholders, but for which biobanks do not have an important role to play.

N13	*How can you permanently motivate people to stay out of the risk zones for fatty liver and NASH? How can we create effective awareness in society?*
N14	*To what extent can first line health professionals, prevention policies (child and family services, school medicine, ...) and other social actors play a role in research into and prevention of fatty liver disease and NASH?*
N15	*Which levers can we activate for prevention of fatty liver disease and NASH among our children and youngsters through sensitization and education?*
N16	*Are the medical guidelines for physicians, including general practitioners, sufficiently elaborated and known so that patients with a high risk of fatty liver disease or patients in the early stages of the disease can be correctly diagnosed and followed-up sufficiently?*
N17	*How can we cure NASH?*
N18	*Research is expensive and not all research can be carried out within the available budgets. How can we select the most useful research? Where do we set priorities and how do we determine who will ultimately finance which research?*
N19	*What is or will be the impact of NASH on healthcare in Belgium?*
N20	*How can we come to a more patient-centered, integrated, multi-care system (cardiovascular, endocrinological, ...) to improve treatment of patients?*
N21	*How to set up a multidisciplinary and integrated research and prevention approach at national and international level to effectively tackle all comorbidities resulting from a Western lifestyle?*

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Working together to set research priorities for NASH with an optimal contribution of biobanks (2018)

Next publications 'Mind the Gap!' :

Benefits and challenges of a multistakeholder dialogue for priority setting in health research: sharing the experience of 3 pilot projects' (2018)

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