Deliverable No. 2.4

Acceptance of hypermodels by patients and physicians

Grant Agreement No.:	600841
Deliverable No.:	D2.4
Deliverable Name:	Acceptance of hypermodels by patients and physicians
Contractual Submission Date:	30/09/2016
Actual Submission Date:	27/10/2016

Dissemination Level		
PU	Public	**X**
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

COVER AND CONTROL PAGE OF DOCUMENT	
Project Acronym:	**CHIC**
Project Full Name:	Computational Horizons In Cancer (CHIC): Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology
Deliverable No.:	D2.4
Document name:	Acceptance of hypermodels by patients and physicians
Nature (R, P, D, O)[1]	R
Dissemination Level (PU, PP, RE, CO)[2]	PU
Version:	1.0
Actual Submission Date:	27/10/2016
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ABSTRACT:

This deliverable analyses the question "How can the acceptance rate of a hypermodel be increased by patients and physicians?". To this end the paradigm of nephroblastoma hypermodel was presented at different congresses and discussed with participants. The Nephroblastoma multimodeler hypermodel has served as a concrete hypermodel but with the aim to generalize the results for other hypermodels as well. In addition, a survey/questionnaire was developed in order to collect feedback from a broader community and other stakeholders. As a result three major points were identified that need to be addressed thoroughly in the future. These are *clinical relevance of hypermodels*, *education and explanation of hypermodels* mainly to physicians but also patients and *validation and certification* of hypermodels.

KEYWORD LIST:

hypermodel, acceptance by patients and physicians, in silico oncology, in silico medicine

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 600841.

[1] **R**=Report, **P**=Prototype, **D**=Demonstrator, **O**=Other

[2] **PU**=Public, **PP**=Restricted to other programme participants (including the Commission Services), **RE**=Restricted to a group specified by the consortium (including the Commission Services), **CO**=Confidential, only for members of the consortium (including the Commission Services)

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MODIFICATION CONTROL			
Version	**Date**	**Status**	**Author**
1.0	15/01/2014	Draft	Norbert Graf
2.0	31/03/2014	Draft	Norbert Graf
3.0	17/04/2014	Draft	Norbert Graf
4.0	20.05.2016	Draft	Norbert Graf
5.0	16.06.2016	Draft	Norbert Graf
5.1	30.06.2016	Draft	Norbert Graf
5.2	15.07.2016	Draft	Norbert Graf
5.3	10.08.2016	Draft	Norbert Graf
5.4	28.08.2016	Draft	Norbert Graf
5.5	17,09.2016	Draft	Norbert Graf
5.6	30.09.2016	Draft	Norbert Graf
5.7	14.10.2016	Draft	Norbert Graf
6.0	25.10.2016	Pre-final	Norbert Graf
7.0	26.10.2016	Final	Norbert Graf

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1 Executive Summary

This deliverable analyses the question of how one can get acceptance of hypermodels by patients and physicians. The nephroblastoma multimodeler hypermodel has served as a concrete hypermodel in this context with the aim to obtain generalizable results for hypermodels in the generic context. . To this end the nephroblastoma hypermodel was presented at different congresses and was discussed intensively with congress participants. Results of these discussions have been analysed in a feedback loop and summarized in a questionnaire that has been widely spread using multiple websites and channels.

The intention of the questionnaire was to collect feedback from a broader community and different stakeholders including patients.

As a result of the congress discussions and the questionnaire based input, three major points were identified that need to be addressed thoroughly in the future, if hypermodels are to be accepted by patients and physicians. These points include *clinical relevance of hypermodels*, *education and explanation of hypermodels* mainly to physicians but also patients and *validation and certification of hypermodels.* A concrete plan for the validation and the certification for hypermodels has been developed and is presented in the conclusions section in this deliverable.

2 Introduction

2.1 Purpose of this document

Particularly in Paediatric Oncology there is a need for better diagnosis and treatment, as conventional approaches including clinical trials have not increased survival rates in many of paediatric cancers during the last decade. Cancer in childhood has an incidence of more than 175,000 per year worldwide, and a mortality rate of approximately 96,000 per year. In high-income countries, approximately 20% of children die. In low resource settings, on the other hand, mortality is approximately 80%, or even 90% in the world's poorest countries. In many countries the incidence is slowly increasing, as rates of childhood cancer increased by 0.6% per year between 1975 to 2002 in the United States and by 1.1% per year between 1978 and 1997 in Europe.

The probability of a successful treatment outcome in paediatric cancer is now high with more than 80% of children surviving their disease in high-income countries. Nevertheless, to increase survival rates for individual patients new methodologies are needed today. Through clinical trials alone one would need extremely large cohorts of patients to increase these survival rates. Even international and multicentre trials are difficult to recruit high numbers of patients in rare diseases as childhood cancer. In addition medicine is undergoing a paradigm shift, which gradually transforms the nature of healthcare from *reactive to preventive*. The changes are catalysed by a new approach to disease that has triggered the emergence of personalized medicine focusing on integrated diagnosis, treatment and prevention of disease in individual patients. The pre-requisites for this are the convergence of systems approaches to disease, new measurement, modelling and visualization technologies, and new computational and mathematical tools[3]. Hypermodels are one of these approaches that shall be used by physicians for decision support.

This deliverable addresses the question: “How to get acceptance of hypermodels by patients and physicians?” This is an important question, as without acceptance by the relevant stakeholders hypermodels will not be used even if they exist. All beneficiaries of the CHIC project discussed this topic during their regular consortium meetings. As an approach to find an answer to this question, two different actions were implemented in the work plan. First one would need to spread the information about hypermodels on scientific congresses especially where clinical stakeholders are present and secondly to develop a questionnaire to collect answers from a broader community with different stakeholders. Based on the evaluation workshops described in D11.3 the answers to the question were found in an iterative way by taking the knowledge of the workshops as a basis for the discussions at the attended conferences and the development of the questionnaire with very concrete questions that emerged during this evolutionary process. In all these activities the nephroblastoma multimodeler hypermodel served as a concrete example of a cancer hypermodel and was presented at the conferences either directly through its technical platform or as a short video along within the questionnaire. Although this hypermodel addressed only one disease and only one question to be answered by the hypermodel, it did serve as an example of understanding what hypermodels are and what can be expected from a hypermodel. The process provided a general answer to the question of how to get acceptance of hypermodels by patients and physicians. The nephroblastoma hypermodel was selected because of the availability of conferences that could be attended by clinical partners of the consortium.

This deliverable describes the efforts that were made and the results that were achieved.

[3] http://www.cra.org/ccc/

3 Conferences to discuss CHIC hypermodels

This chapter describes how acceptance of hypermodels was discussed at different medical conferences. In addition to the described conferences in this deliverable the second evaluation workshop round created first impressions on how hypermodels will be accepted by the target group. The results of the second evaluation workshop are described in detail in deliverable D11.3 and reports on two workshops. The first was held in Söllereck, Oberallgäu in Germany from the 9th to the 13th of January 2016. The second one took place during the 9th International Renal Tumor Biology Conference in Toronto, Canada from the 2nd to the 3rd of April 2016. The most important objective of this workshop round was the question whether the nephroblastoma hypermodel, as a test of principle, can serve as a clinical decision support tool for paediatric oncologists in the future. This question also deals with the acceptance of hypermodels. Results were encouraging and presented in detail in D11.3. In addition, these two evaluation workshops served as a background for the two clinical conferences described in this deliverable. The CHIC platform was presented in these clinical conferences to a much broader spectrum of stakeholders, so that results can be more easily generalized.

3.1 International Conference and Exhibition on Pediatric Oncology and Clinical Pediatrics

From August 11th to August 13th 2016 the 'International Conference and Exhibition on Pediatric Oncology and Clinical Pediatrics' took place in Toronto, Canada.

The conference was organized with the aim to invite people to become familiar with paediatric oncology related tools that are available today, their cost, how they are used at other institutions and how they can be used in one's research or projects. The target audience included the following stakeholders:

- Paediatric Oncology Students, Scientists
- Paediatric Oncology Researchers
- Paediatric Oncology Faculty
- Medical Colleges
- Paediatric Oncology Associations and Societies
- Business Entrepreneurs
- Training Institutes
- Pharmaceutical Manufacturing Companies
- Software Developing Companies
- Data Management Companies
- Paediatric Oncology Physicians

This conference as a global platform allowed discussing and learning about Pediatric Oncology in all aspects, including the different cancers, their diagnosis, treatment and follow-up. The main theme of the conference is*: '**Benchmark practices and accelerating computational approaches for Pediatric Oncology**'*. In this respect the conference was ideal for the CHIC project to demonstrate and disseminate results of the project to the target audience as given in the report below.

The final scientific program of the conference can be downloaded here:
http://pediatriconcology.conferenceseries.com/pdfs/pediatric-oncology-2016-final-program.pdf

CHIC organized and integrated a workshop on the Oncosimulator and cancer hypermodelling that took place on the second day of the conference. The CHIC workshop was centred around the theme:

"Combining clinically driven and clinically oriented multiscale cancer modelling with information technology in the in silico oncology context."

Members of the CHIC consortium gave the following lectures:

Norbert Graf:	CHIC (Computational Horizons in Cancer) - Perspective from the clinical side
Georgios Stamatakos:	Computational Horizons in Cancer (CHIC): Developing meta- and hyper-multiscale models and repositories for in-silico oncology – Strategies, systems and results
Marc Stauch:	The law and in-silico health technology: Help or hindrance?
Ravi Radhakrishnan:	In silico oncology- Computational horizons in cancer systems biology and multi-scale cancer modelling
Daniel Abler:	CHIC-CDR: A repository for managing multi-modality clinical data and its application to in-silico oncology
Kostas Marias:	Integrating CHIC technologies into a clinical research application framework ("CRAF") for cancer modelling

The multimodeler hypermodel for nephroblastoma was demonstrated and discussed with the audience to get feedback, answering the questions shown in Appendix 2 that are included in the following chapter.

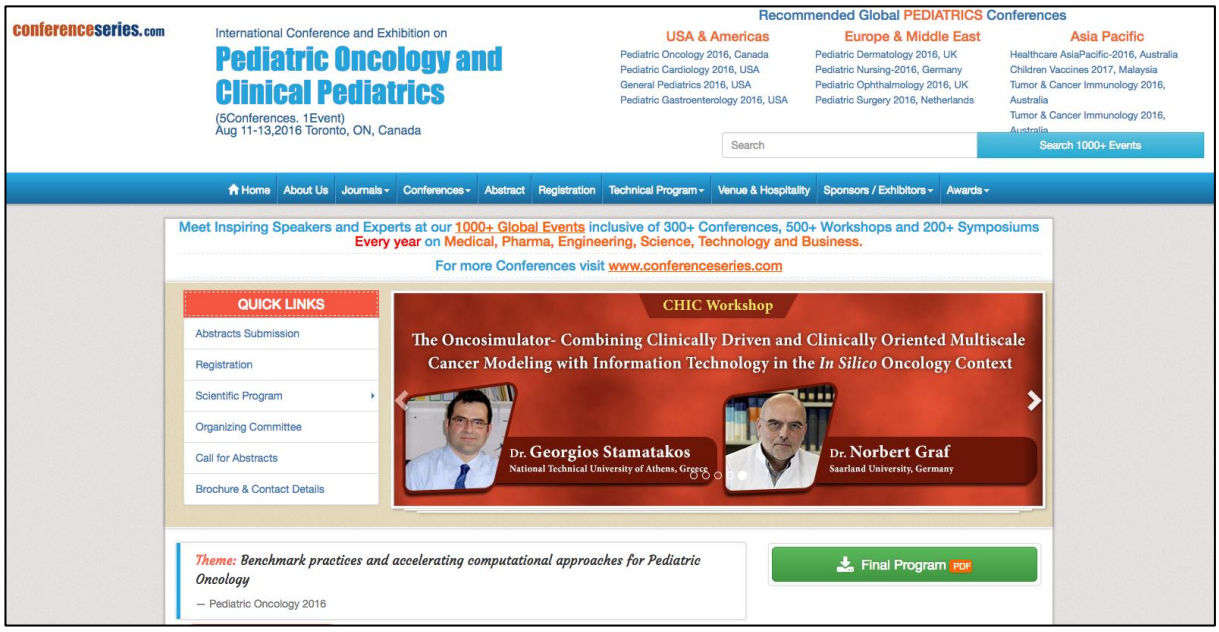

Fig. 3.1: Website announcing the CHIC workshop of the conference: http://pediatriconcology.conferenceseries.com/2016

3.1.1 Important feedback points concerning the CHIC platform

- ✓ Numerous questions were asked by the participants (mostly clinicians) in order for them to better understand various aspects of the CHIC systems and their prospective clinical use.
- ✓ An enthusiastic appreciation of the potential of the CHIC systems, approach and strategy for Paediatric onoclogy, clinical pediatrics and clinical medicine at large was expressed. The official report of the conference (see next chapter) specially refers to "*the excellent session of workshop which captured the attention of the audience*"
- ✓ Questions regarding the cost of and the accessibility to the CHIC clinical decision support systems by clinicians in less developed or developing counties, when fully clinically validated, were asked and answered.
- ✓ The importance of the user interface for the clinician who is not familiar with software technology was stressed by conference participants
- ✓ Further interactions with a number of interested conference participants in the context of CHIC were initiated.

3.1.2 Pediatric Oncology 2016 Report

A report of the conference is provided by the organizers and can be found at: http://www.conferenceseries.com/Past_Reports/pediatric-oncology-2016-past.

Here is the text of this report:

"International Conference and Exhibition on Pediatric Oncology and Clinical Pediatrics organized by Conference Series LLC was successfully held at Holiday Inn Toronto Airport, Canada during August 11-13, 2016. The conference was organized around the theme "*Benchmark practices and accelerating computational approaches for Pediatric Oncology*".

Active participation and generous response were received from the Organizing Committee Members of Conference Series LLC as well as from renowned speakers, eminent Scientists, Talented Researchers and Young Student Community. Researchers and students who attended from different parts of the world has made the conference one of the most successful and productive events in 2016 from Conference Series LLC. The conference was marked with the presence of renowned scientists, talented young researchers, students and business delegates driving the three days event into the path of success with thought provoking keynote, special workshop, plenary speeches and poster presentations.

Pediatric Oncology-2016 Organizing Committee would like to thank the Moderator of the conference, Imke Bartelink, University of California, USA and Georgios Stamatakos, National Technical University of Athens, Greece who contributed a lot for the smooth functioning of this event.

The conference was initiated with a warm Welcome Note and the Keynote Forum. The conference proceedings were carried out through various scientific-sessions and plenary lectures, of which the following topics were highlighted as Keynote-presentations:

- "The onco simulator - Combining clinically driven and clinically oriented multi-scale cancer modelling with information technology in the in-silico oncology context", by Dr. Georgios Stamatakos, National Technical University of Athens, Greece
- "Drug measurements at the pharmacological target site for individualized pediatric cancer treatment", by Dr. Imke Bartelink, University of California, USA

- "Guiding precision and personalized oncology using multiscale computational models" by Dr. Ravi Radhakrishnan, University of Pennsylvania, USA
- "Overview on pediatric cancers oncolytic viruses and parvovirus B19 may be oncolytic in leukemic children", by Dr. Janak Kishore, Sanjay Gandhi Post-Graduate Institute of Medical Sciences, India

Conference Series LLC extends its warm gratitude to all the Honorable Guests of Pediatric Oncology 2016:

- Dr. Norbert Graf, Saarland University, Germany
- Dr. Georgios Stamatakos, National Technical University of Athens, Greece
- Dr. Elizabeth Algar, Hudson Institute of Medical Research, Australia
- Dr. Annick Beaugrand, Federal University, Brazil
- Dr. Gehan Lotfy Abdel Hakeem, Minia University, Egypt

We are also thankful to all the Speakers who made this event a grand success and our special thanks to Dr. Norbert Graf and Dr. Georgios Stamatakos for organizing the excellent session of workshop which captured the attention of the audience.

Conference Series LLC acknowledges and appreciates the perpetual support from the Chair and Co-chair, Speakers, Business Delegates, Students, and Media Partners. We are glad to inform that all accepted abstracts for the conference have been indexed in Omics International journal, the *Journal of Pediatric Therapeutics 2016* as a Special Issue.

We are also obliged to various delegate experts, company representatives and other eminent personalities who supported the conference by facilitating active discussion forums. We sincerely thank the Organizing Committee Members for their gracious presence, support and assistance towards the success of Pediatric Oncology-2016.

With the unique and affirmative feedbacks from the conference, Conference Series LLC would like to announce the commencement of the 2nd International Conference and Exhibition on Pediatric Oncology which will be hosted in Philadelphia, Pennsylvania, USA during August 28-30, 2017. *Let us meet again @ Pediatric Oncology-2017.*"

3.1.3 SIOP 2016 International Conference

Between October 19th to 22nd 2016 the 48th Congress of the International Society of Paediatric Oncology (SIOP) took place in Dublin, Ireland.

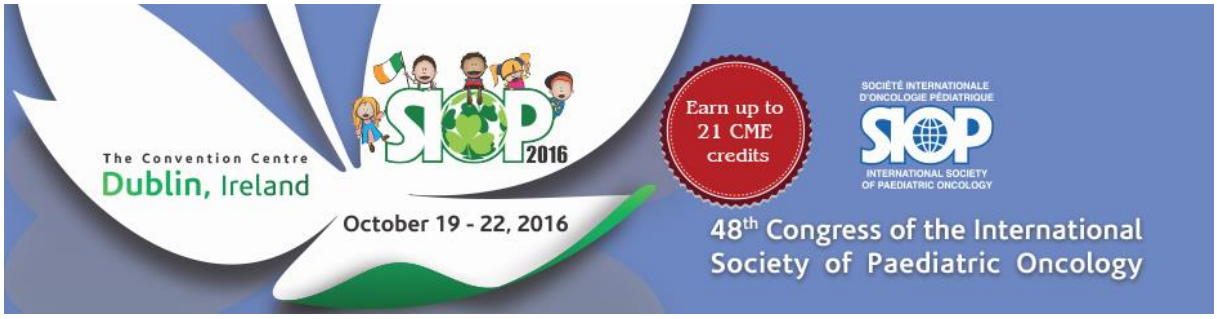

Fig. 3.2: Website announcing the 48th Congress of SIOP in Dublin (http://siop2016.kenes.com/).

SIOP's aim is to improve and optimise treatments throughout the world. SIOP's vision is that no child should die of cancer.

A high quality scientific programme covering almost all aspects of paediatric oncology, from basic science to clinical studies was produced and delivered. The programme consisted of plenary sessions, guest lectures, committee/group sessions, "Meet the expert" sessions, and free and proffered paper sessions,. New to the SIOP congress was the incorporation of sessions specifically geared towards Young Investigators. SIOP 2016 was the global meeting place for physicians, researchers, scientists, other healthcare professionals and parent groups as well as survivors of paediatric cancer in the field of paediatric oncology and its sub-specialties. Because of the diverse, clinically focused educational offering, participants were able to tailor the curriculum to meet the needs of international clinicians of all levels of experience. Including the perspective of patients and parents.

At the conference Norbert Graf presented and discussed an ePoster entitled: ***A MULTISCALE HYPERMODEL TO PREDICT THE NEPHROBLASTOMA RESPONSE TO PREOPERATIVE CHEMOTHERAPY***, authored by participants of CHIC from all beneficiaries (Fig. 3.3).

During the discussion the audience attending the ePoster demonstration were very interested in the CHIC platform and the nephroblastoma hypermodel. Most of the questions were related to validation and certification of the model and to the possibility for usage in other diseases. Nevertheless there was a clear skepticism in usage the hypermodel in the future, as the prediction of the nephroblastoma hypermodel has not been validated as yet.

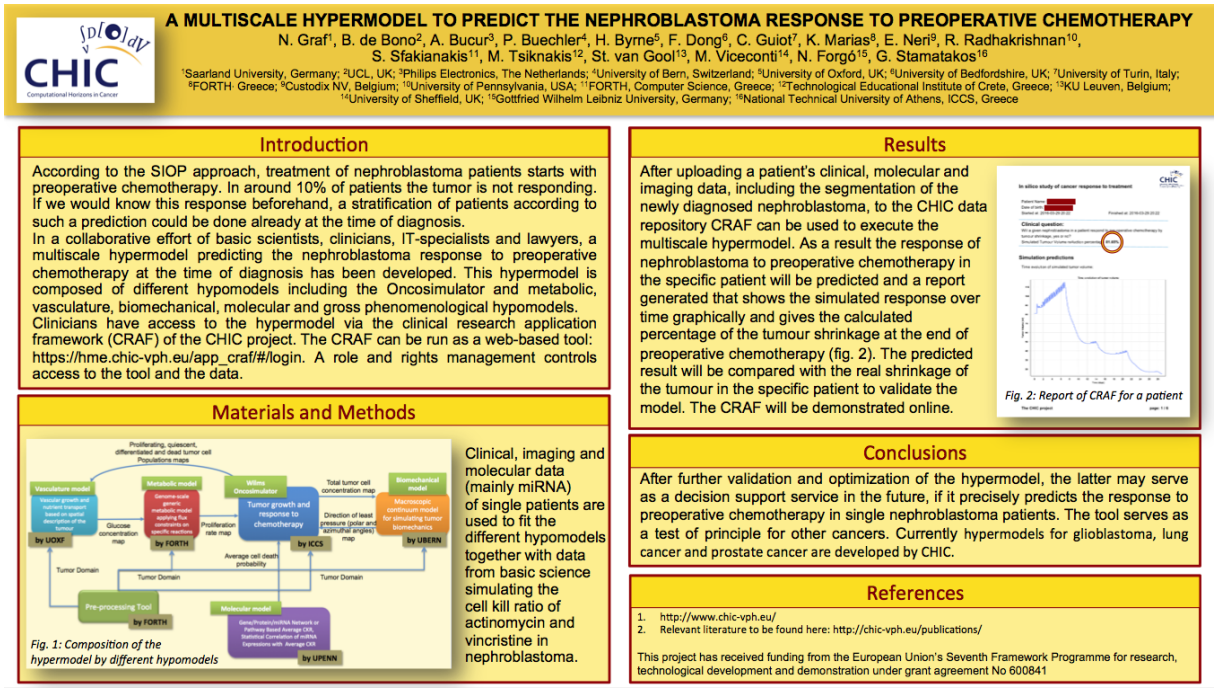

Fig. 3.3: ePoster presented at the SIOP conference in Dublin.

For validation purposes it was proposed that the tool should be used as a new developed drug, going through different clinical trial phases before approval on the market. Phase I should be used to demonstrate that the model is reproducible and that the software behind is without errors. In phase II one needs to demonstrate that the prediction of the hypermodel is accurate showing the real response to treatment in case of the ***nephroblastoma hypermodel***. If phase II is successful one will

be able to conduct a phase 3 trial where conventional treatment is randomised against the treatment predicted by the tool. In case that the hypermodel is beneficial for the patient, the use of the hypermodel would become standard of care for the disease it was tested. Further surveillance of the hypermodel is needed as is the case for phase IV in drug development. Such a scenario was intensively discussed and preferred by the audience of clinicians in order to trust the hypermodels predictions. The main reason for this was the link to drug development that every physician knows and accepts. The open question will be, if regulatory bodies can accept such a procedure for hypermodel approval and certification. If the certification process needs to be done in another way then all the clinicians taking part in this discussion are convinced that acceptance of hypermodels and usage in clinical care would take more time, would be more expensive and can not be done by academics but only by industry.

Participants of the ePoster discussion were also asked to fill in the CHIC questionnaire for the acceptance of hypermodels that is described in Chapter 4 and given in Appendix 1. Their answers are included in the results of this questionnaire.

4 CHIC questionnaire for the acceptance of hypermodels

This chapter describes the use of a questionnaire to collect feedback from the target group of patients and clinicians on how to get acceptance of hypermodels. The questionnaire was distributed throughout different Internet channels. A short educational video demonstrating the multimodeler hypermodel at the beginning of the questionnaire was developed as a starting point of the questionnaire to explain hypermodels. This allowed receiving answers also from people who had never heard about hypermodels. The following chapter describes the results of the questionnaire.

4.1 Results of the CHIC questionnaire for the acceptance of hypermodels

The questionnaire for the acceptance of hypermodels was developed for the SIOP conference and for spreading the information about hypermodels to the scientific community to collect their feedback. Figure 4.2 shows the first page of the online available questionnaire with the starting point of the educational video about the nephroblastoma multimodeler hypermodel. Details of the questionnaire are given in Appendix 1.

The questionnaire can be answered online via different links. An English and a German version of the questionnaire can be selected. The questionnaire is still online and answers can still be given. You can find the two different versions directly via the following links:

English: http://www.ehealthserver.com/survey/index.php?r=survey/index&sid=423562&lang=en
German: http://www.ehealthserver.com/survey/index.php?r=survey/index&sid=423562&lang=de

The questionnaire is also linked to the CHIC Homepage and distributed via eCancer.

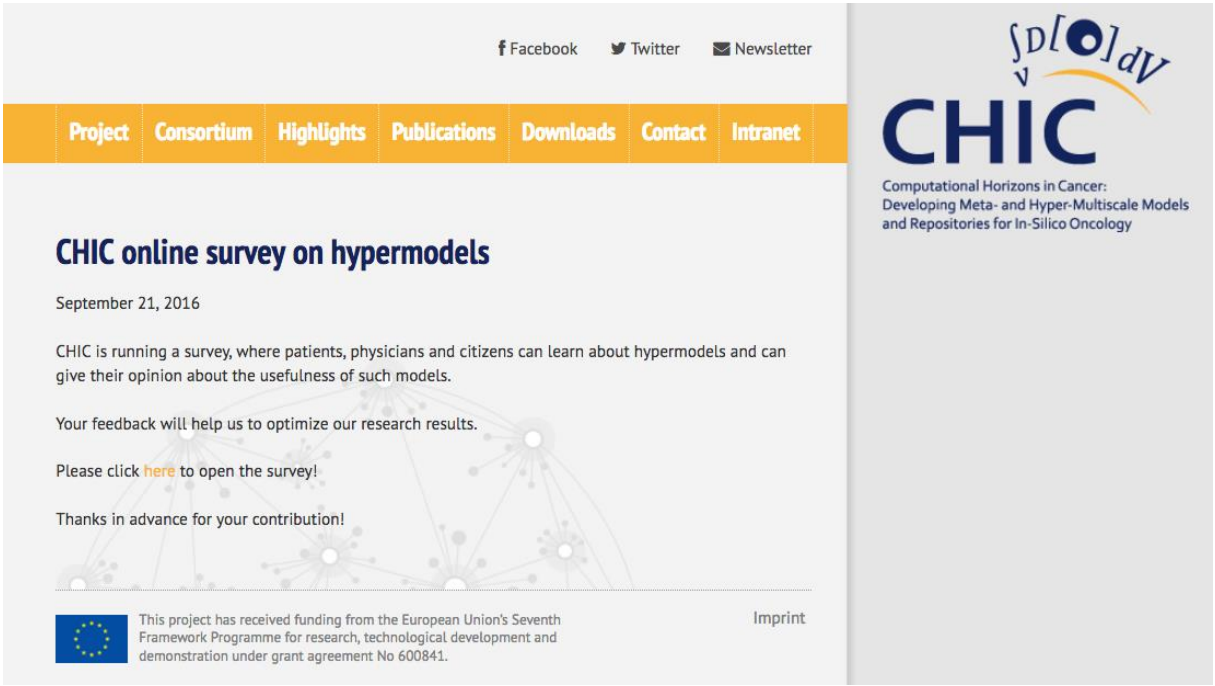

Fig. 4.1: Screenshot of the CHIC homepage announcing the questionnaire for the acceptance of hypermodels.

Fig. 4.2: Screenshot of the CHIC questionnaire for the acceptance of hypermodels. Shown is the first page with the short video to demonstrate the nephroblastoma multimodeler hypermodel.

Altogether 39 people answered the questionnaire. The respondents came from 17 different countries. 5 people did not indicate their nationality (Table 4.1). The table shows that people from Belgium and Germany had the most responders. As the number is still small the questionnaire remains online and new attempts are done to attract further stakeholders.

Country	Number of responders	Percentage of responders
Angola	1	2.56%
Argentina	1	2.56%
Belgium	8	20.51%
Brazil	1	2.56%
Canada	2	5.13%
Czech Republic	1	2.56%
Estonia	1	2.56%
Finland	2	5.13%
France	2	5.13%
Gabon	1	2.56%
Germany	5	12.82%
Greece	1	2.56%
Hong Kong	1	2.56%
Ireland	1	2.56%
Italy	2	5.13%
Sweden	2	5.13%
United Kingdom	2	5.1%
Unknown	5	12.82%

Tab. 4.1: Countries where respondents live.

The age distribution is given in the following table (Table 4.2).

Age [years]	Number	Percentage
< 20	0	0.00%
20 - 35	7	17.95%
36 - 45	7	17.95%
46 - 55	10	25,64%
56 - 65	8	20.51%
> 65	2	5.13%
No answer	5	12.82%

Tab. 4.2: Age distribution of respondents.

Interestingly more than half of the patients are older than 45 years. This shows that people of this age group are also interested in hypermodels.

Figure 4.3 shows the gender distribution. More males than females have responded. 6 people did not want to disclose their gender.

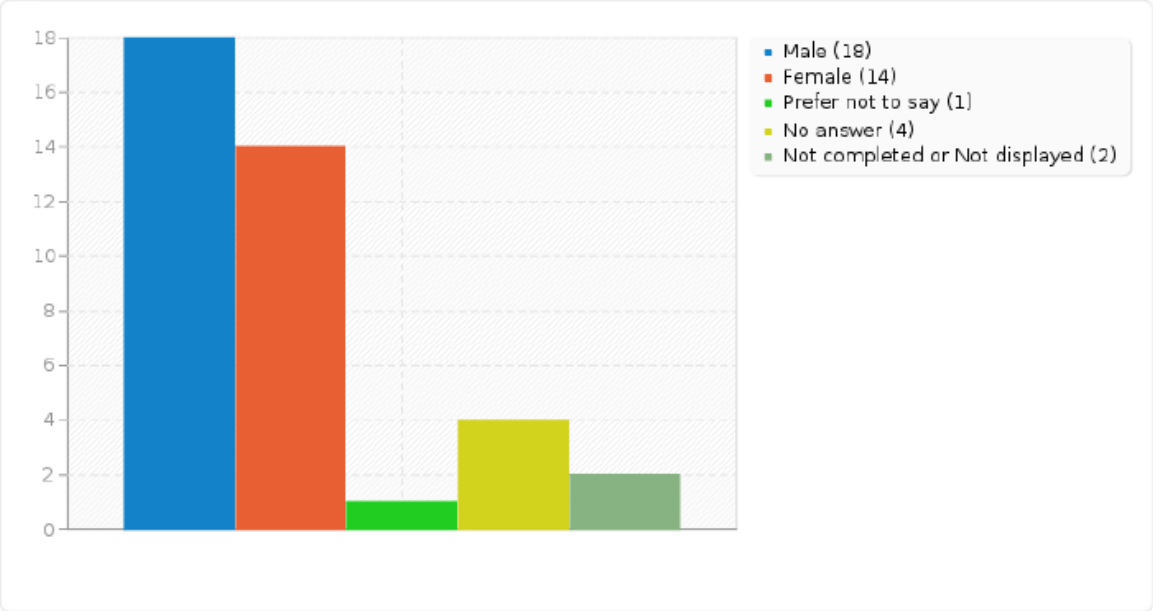

Fig. 4.3: Gender distribution of respondents.

The health condition of most of the respondents was good to excellent. Only 2 respondents had a fair health condition (chronic disease) and 6 did not answer or complete this question. (Fig 4.4)

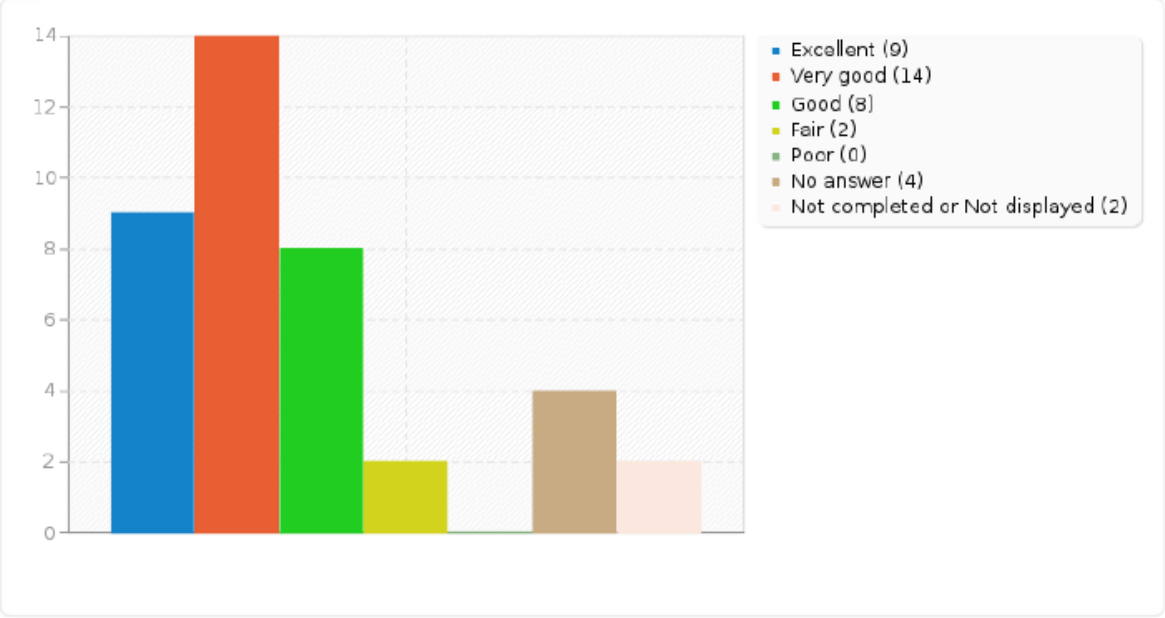

Fig. 4.4: Gender distribution of respondents.

Most of the respondents (30) had a University degree showing that the group of responders is highly educated and may understand the hypermodels much better than less educated people.

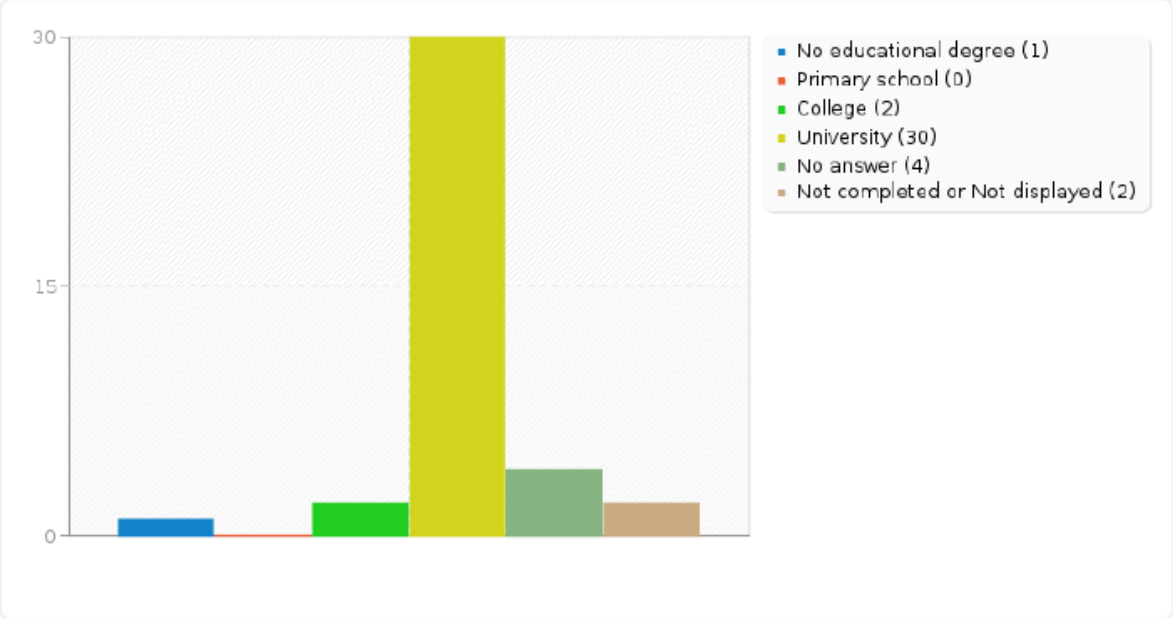

Fig. 4.5: Distribution of the educational degree of respondents.

In addition 33 of the responders are employed. Only one person is unemployed.

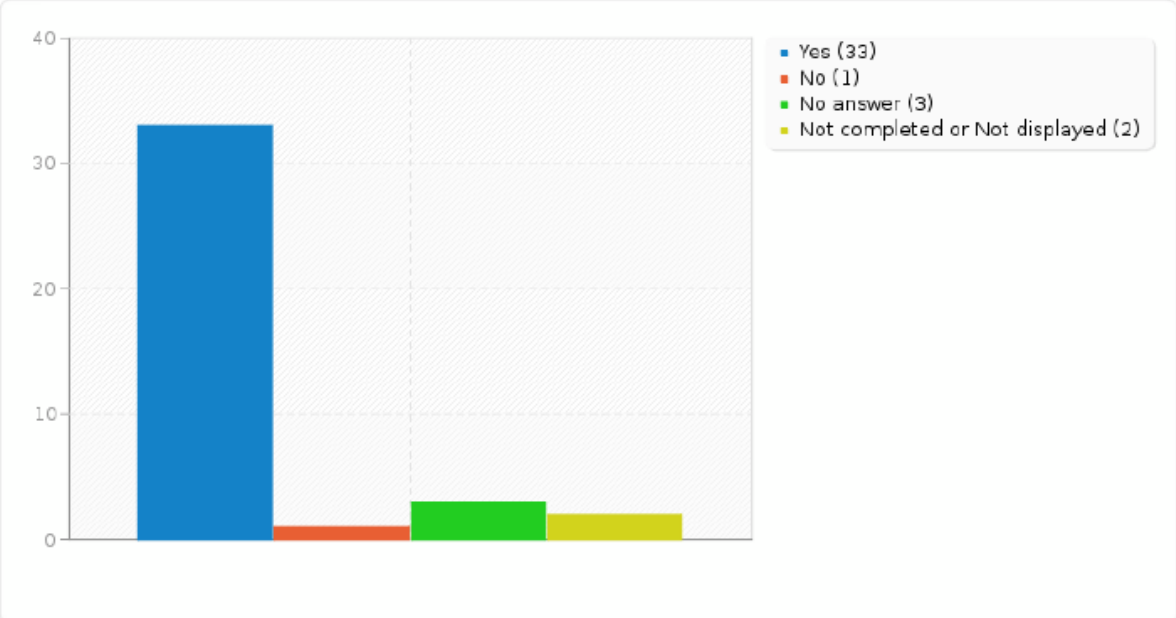

Fig. 4.6: Distribution of employment of respondents.

Many of the responders (17) are working in healthcare. Twelve of them are physicians. Nine are basic researchers and four work in the IT sector.

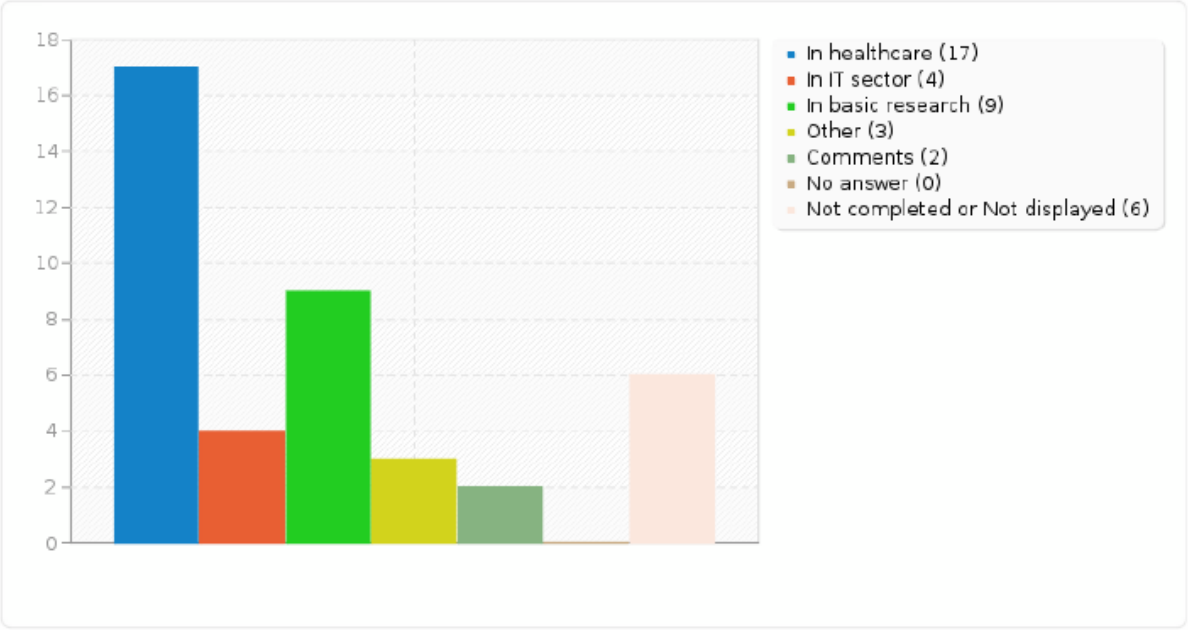

Fig. 4.7: Distribution of professions of respondents.

Nearly half of the responders (17) had not heard about hypermodels despite their high education level.

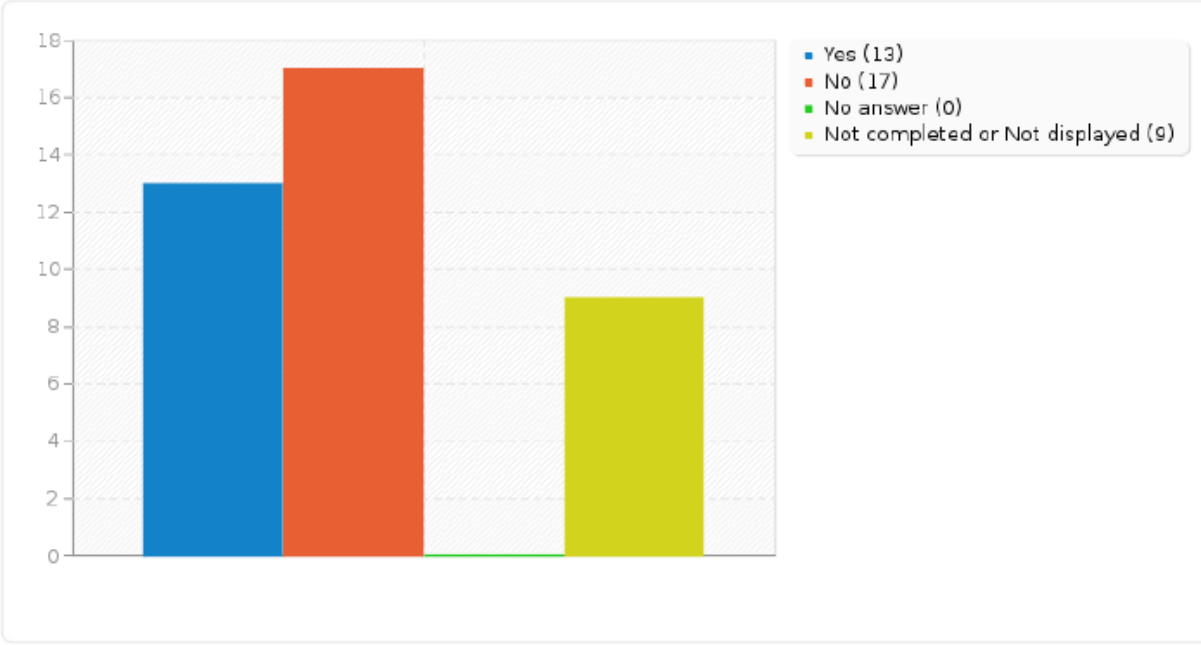

Fig. 4.8: Hypermodel knowledge of respondents.

The introductory educational video presented at the beginning of the questionnaire was helpful for most (25) of the respondents, so that they did understand hypermodels.

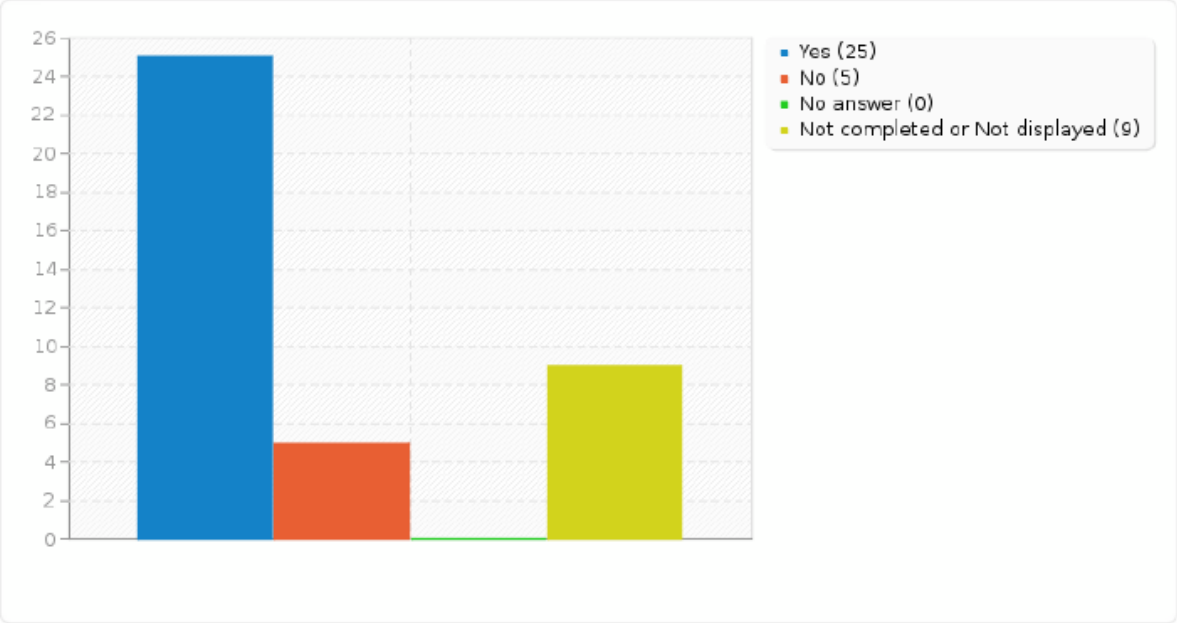

Fig. 4.9: Understanding of hypermodel after watching the introductory educational video.

Most of the responders (29) would allow their physician to use their data for running the hypermodel. Only one person does not allow the usage of his/her data for that purpose.

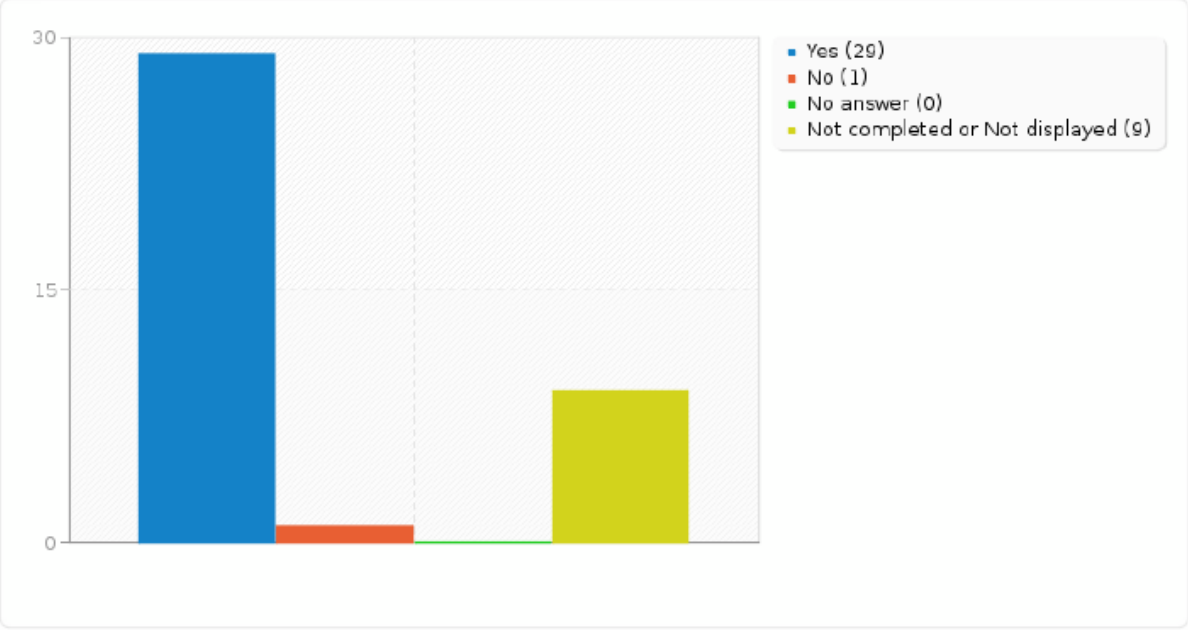

Fig. 4.10: Permission of use of the responders' data by their physician.

Interestingly, nearly half of the responders trust the prediction of the hypermodel whereas nearly the other half do not trust the prediction of hypermodels as given in figure 4.11.

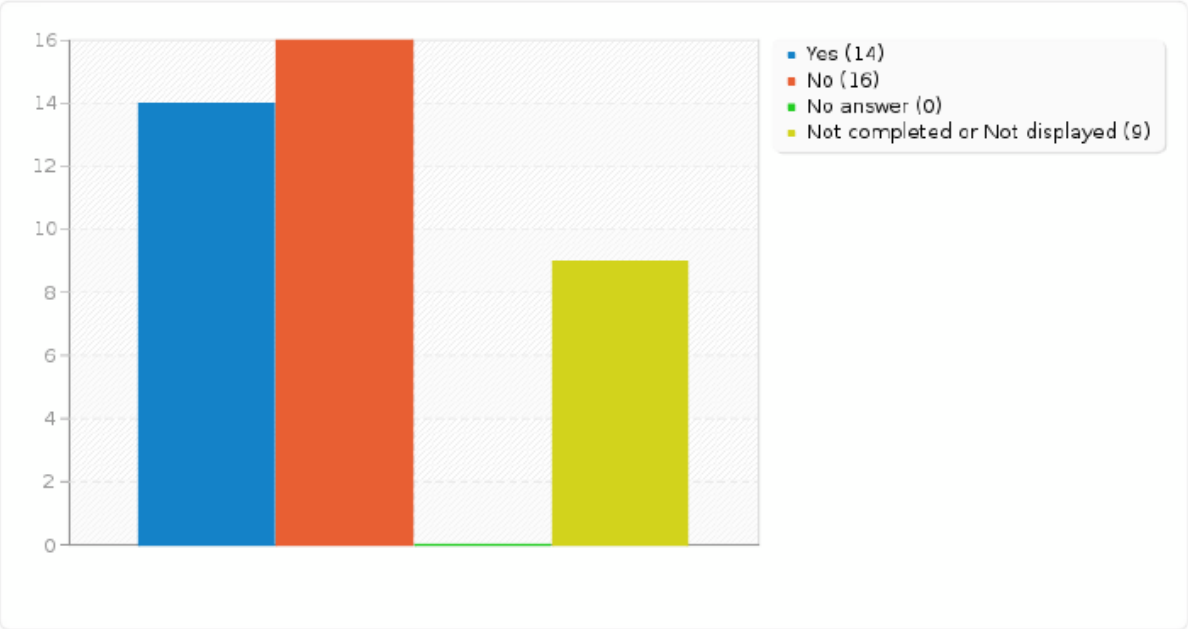

Fig. 4.11: Trust in the prediction of the hypermodel.

26 responders answered the question 'What will increase your trust in hypermodels. The "raw" answersare given here:

- More validation of the hypermodel
- Experience
- Unter anderem: EBM-basierte Evaluation der Hypermodelle durch unabhängige Institutionen ohne ökonomisches Interesse an der Patientenversorgung/ Leitlinien-Ausgestaltung. Verlinkung HC Datenmodelle mit Versorgungsforschung QoL-Modelle
    - Translation: Besides other points an EBM-based evaluation of hypermodels through independent organizations without economic interests in patient care or guideline development is necessary. Linkage to HC data models with patient centred research and quality of life models.
- A clearer explanation of the background context, and what the models will contribute over and above existing standard clinical - this did not seem clear from the video. E.g. is the clinician using them as a form of clinical decision support? If so, will there be some independent checking of the models, such as by a medical devices agency, that they give accurate predictions?
- Validation of the hypermodel
- To understand them
- Knowing the basic science behind
- After validation of the hypermodel
- Knowing the basic science behind and understand it

- More validation
- Showing that the hypermodel is validated
- Showing validation results
- There needs to be more experience in the clinical setting
- There needs to be more validation, medical device law needs to respected, certification is missing
- Validation and certification
- Needs to be certified
- Validation and certification
- I do trust
- Missing validation
- Too new, I need to understand more
- If the tool will be certified
- If it can be shown that it is helpful in other patients
- Need to see a study demonstrating the benefit
- Need to see the benefits by knowing how this hypermodel will make treatments better
- Validation is needed
- Positive feedback from patients that are treated according to the prediction of the hypermodel

Mostly validation and certification of hypermodels are given as arguments to increase the trust in hypermodels. In addition, more background information is requested to understand the benefit of hypermodels in comparison to standard clinical care. If the physician of the respondent would trust in hypermodels 28 of the responders would also trust and only two would not trust the prediction of the hypermodel (Fig. 4.12)

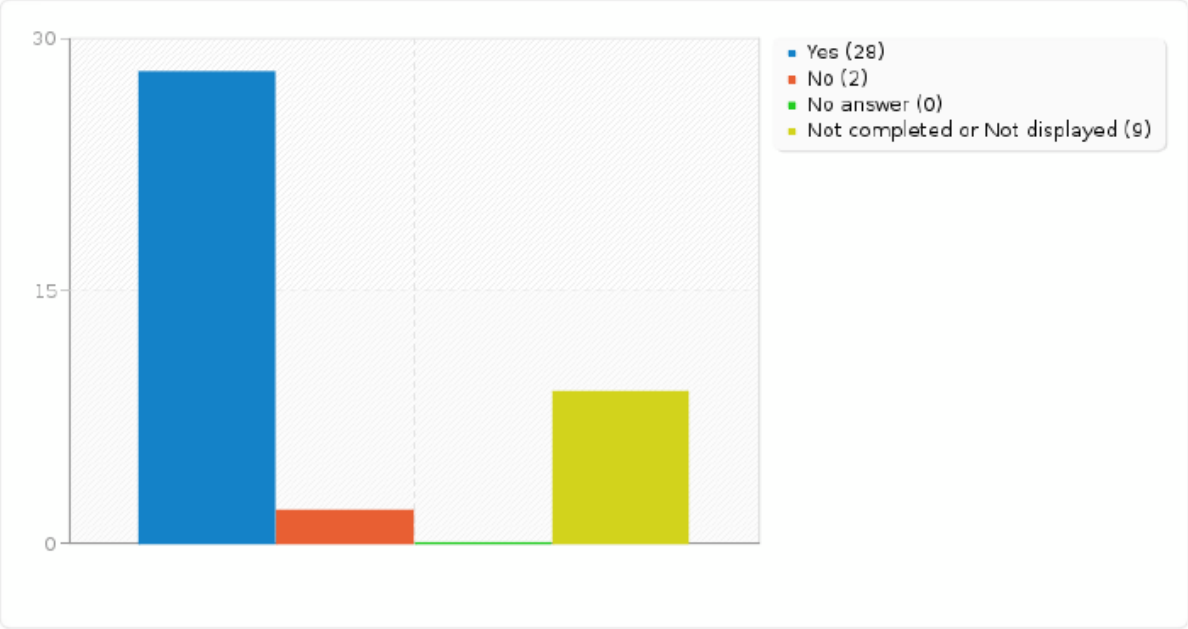

Fig. 4.12: Trust in the prediction of the hypermodel if the physician of the respondent would trust.

The question: 'If your physician is using a hypermodel with your individual data and would like to treat you according to the prediction of the hypermodel, would you like to be treated accordingly?' was answered 25 times with yes (Fig. 4.13). This shows a high trust in the physicians of the responders and underpins an important role of physicians in the process of acceptance of hypermodels.

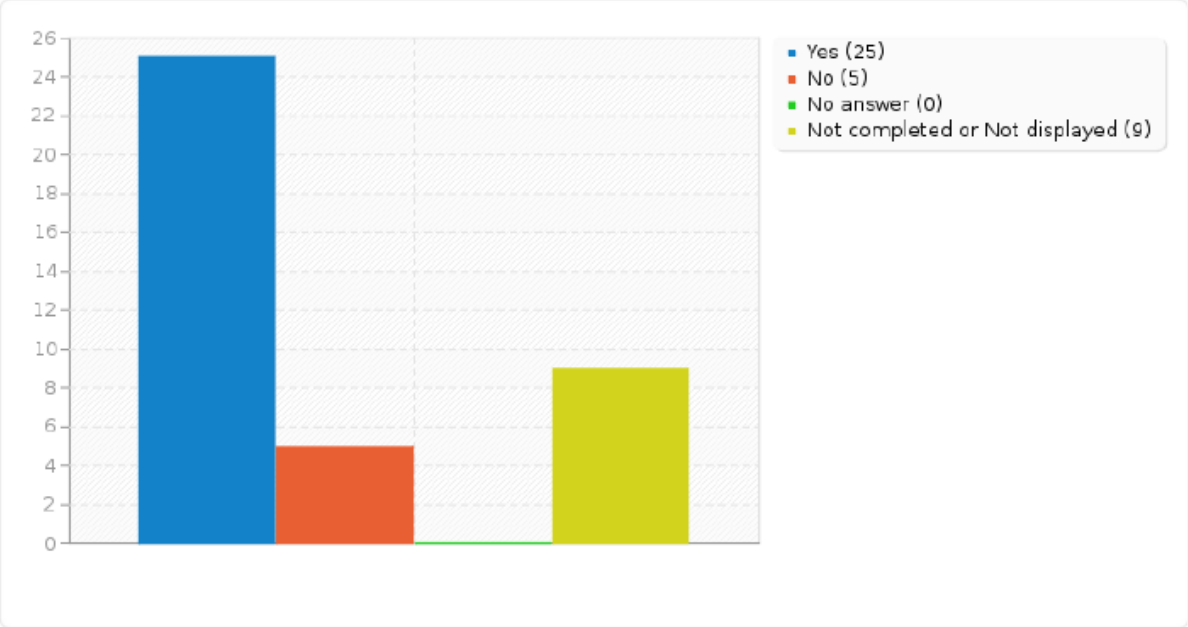

Fig. 4.13: Treatment according to the prediction of the hypermodel if the physician uses the data of the respondent.

The responders, who did not want to be treated according the prediction of the hypermodel, gave the following answers:

- Wissenschaftliche Evaluation seines "Modells" bleibt mir unklar; es drohen ähnliche Probleme wie bei Leitlinien-Entwicklungen (Versorger- statt Patientenorientierung)
  - Translation: The scientific evaluation of the model remains unclear to me; there might come up same problems as seen in guideline developments (patient provider than patient orientation)
- I would first like to know more about how the hypermodel arrives at its specific prediction for me, and whether its accuracy has been independently tested and evaluated by an external certifying agency.
- I need to understand the basics behind

These answers explain that more knowledge needs to be given to patients and physician about hypermodels. Therefore education and teaching is an important issue in the process of acceptance of hypermodels.

The information about successful treatment of other patients according to the prediction of hypermodels would be helpful for only 4 responders. But most of the responders (34) did not answer this question.

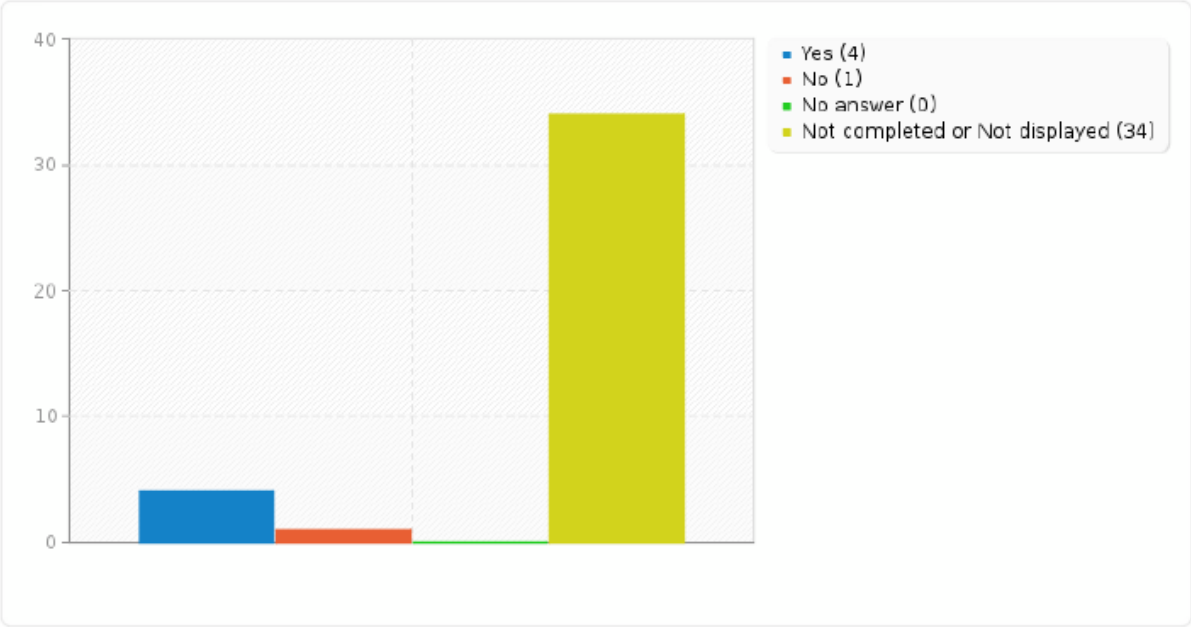

Fig. 4.14: Help of successful treatment of other patients according to the prediction of the hypermodel.

Three responders answered the question " What could additionally be done in order for a patient to allow to be treated according to the prediction of a hypermodel. Their answers are listed here:

- Wissenschaftlich-neutrale Evaluation (IQTIG? Cochrane? FDA?)
  - Translation: Scientific neutral evaluation (IQTIG? Cochrane? FDA)
- See comments in the previous block; it would be generally useful to receive more explanation of why hypermodels in their predictions may offer an improvement over the human judgment of the treating clinician.
- To see validation results

26 responders explained what a treating physician can do to increase the trust in the prediction of hypermodels. Here are their "raw"' answers:

- To explain me the advantages of the hypermodel
- Having all the date in place

- Nachweis persönlicher Aus- und Fortbildung in diesem Thema offenlegen
  - Translation: Show the proof of personal training and education in this area
- Explain why s/he has professional confidence in the accuracy of the hypermodel. (I think that if s/he could not do this, but at the same time was trying to persuade me the hypermodel should be used in my case, I might well lose trust in the physician.)
- Explain me the hypermodel
- He needs to explain me the details of the hypermodel and why it is better than standard care
- Explaining me my disease
- He needs to explain me the basics behind
- He needs to be able to explain me the background behind
- Showing me that other patients were treated successfully according the prediction of the hypermodel
- Speak with me
- He should use the prediction of the hypermodel for his own disease
- To provide me with scientific background (papers, online info, etc.)
- Demonstrating the benefit of the hypermodel for my disease
- Explain the hypermodel and the benefit for getting a better treatment
- Needs to show me that he is trusting in the hypermodel
- Explain the scientific behind
- Do not know
- Nothing can be done by the physician
- Explain me the tool in detail
- He can do nothing
- Needs to demonstrate that treatment is better than without the help of the hypermodel
- Clinical trial needs to show the benefit of the hypermodel
- Nothing
- Nothing
- Being convinced by himself that the tool is beneficial page

Again trust in prediction can be achieved by explanation and education about hypermodels and their validation and certification. This is true for physicians and patients.

Most of the responders (28) are convinced that hypermodels will be used by physicians in the future.

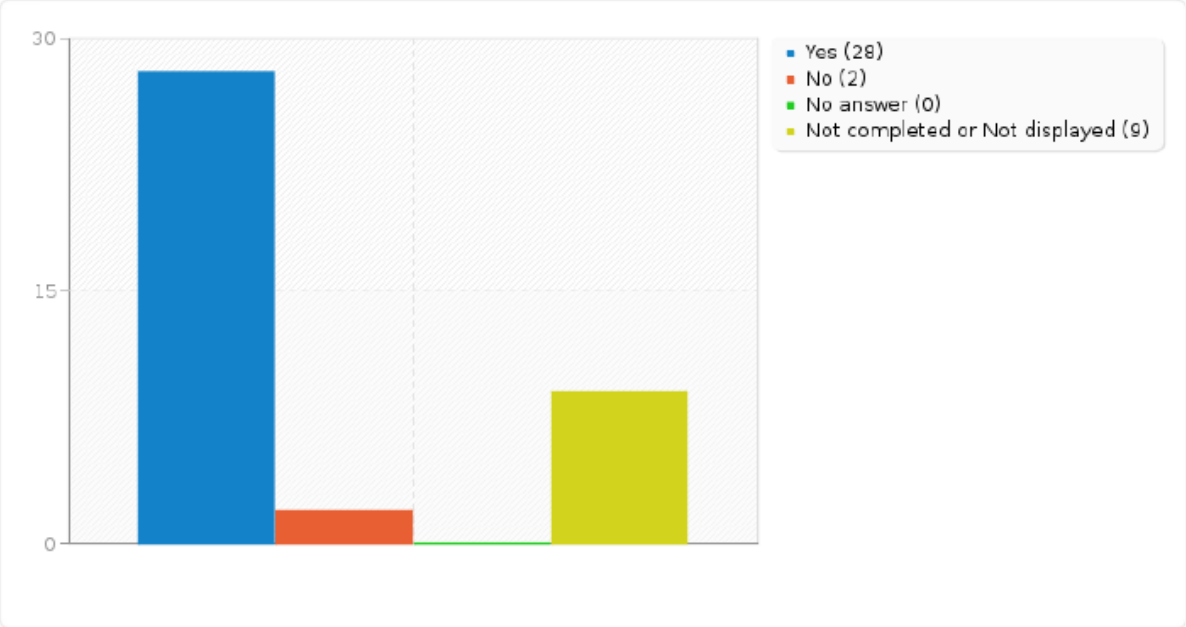

Fig. 4.15: Usage of hypermodels in the future.

Interestingly 28 of the responders would try the hypermodel for their disease, if it would exist, to see the result of the hypermodel prediction.

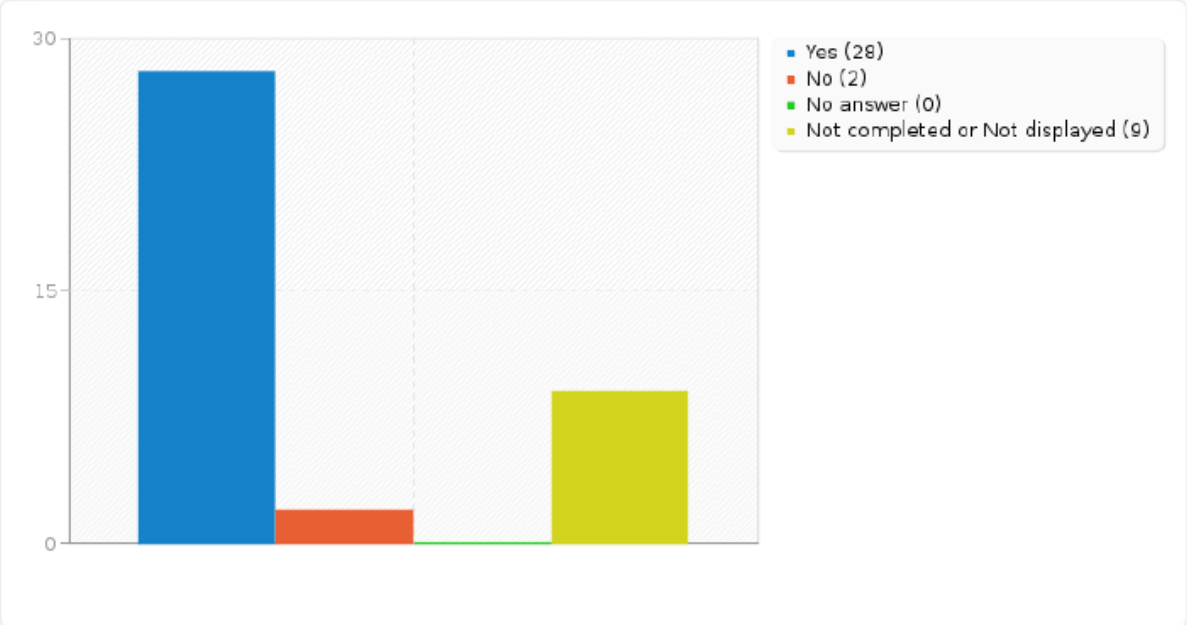

Fig. 4.16: Usage of hypermodels by themselves to see what the prediction will be.

And even more interestingly, 18 of the responders would also start treatment according to the prediction of the hypermodel. On the other hand 10 would not do so.

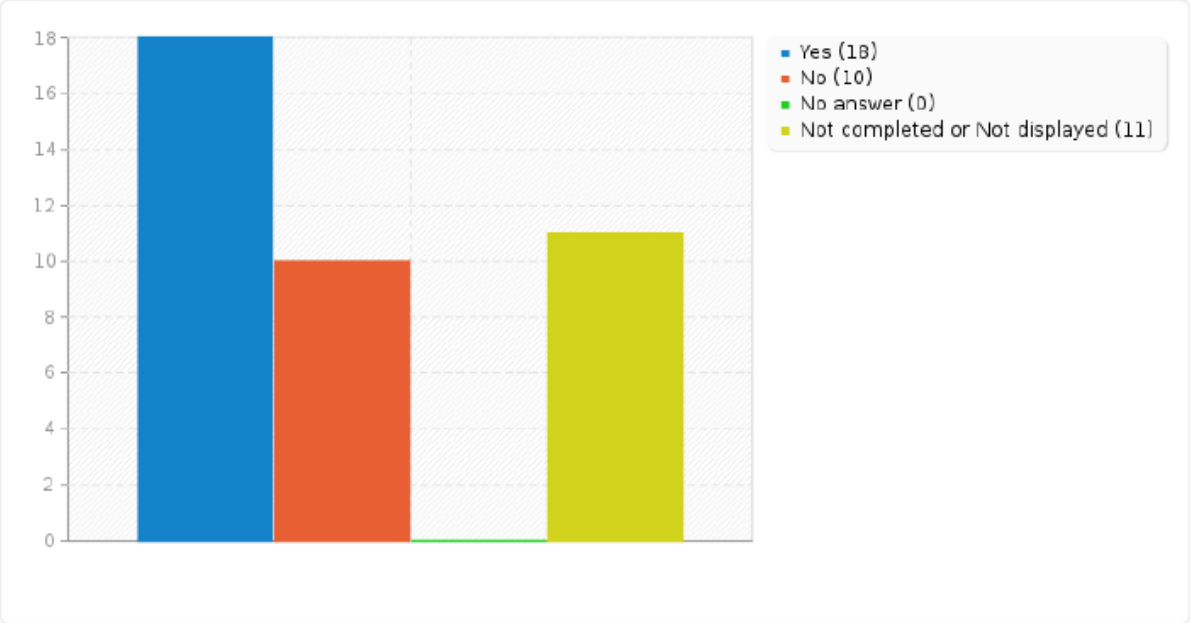

Fig. 4.17: Treatment according to the prediction of a hypermodel by a user.

75 % (29) of responders think that a hypermodel is helpful to explain their disease and response to treatment (Fig. 4.18).

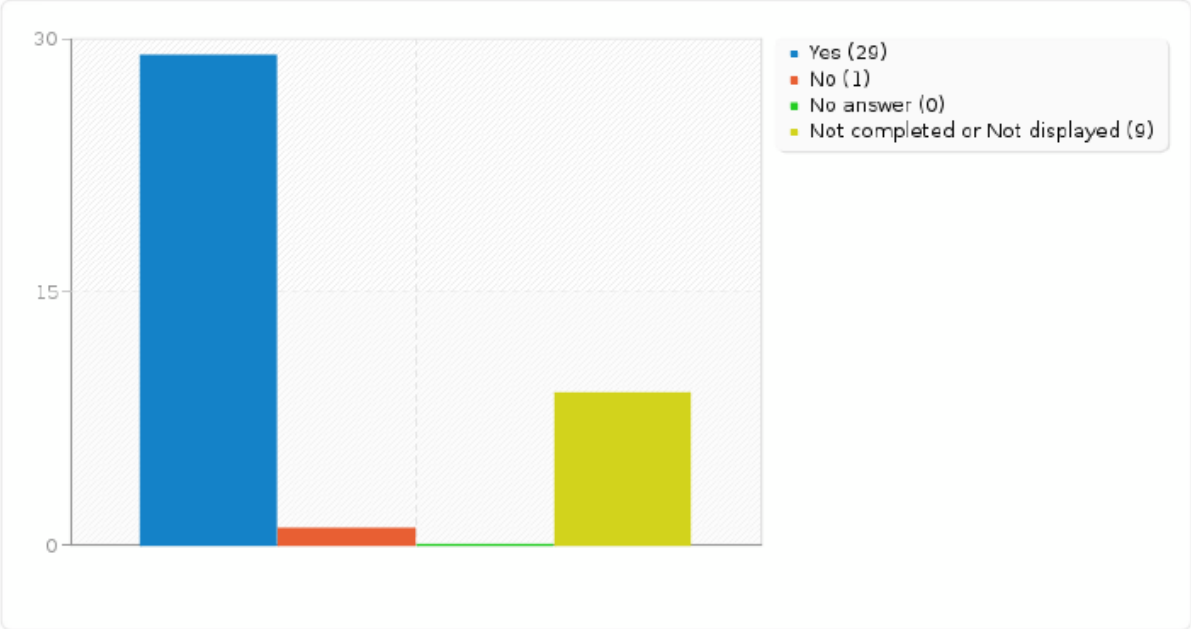

Fig. 4.18: Are hypermodels helpful as an educational tool?

This question shows that hypermodels might also be helpful in explaining diseases and treatments by showing predictions of hypermodels.

Only two respondents want to get feedback about the results of the questionnaire. They provided their email addresses.

5 Conclusion

In order to collect information on how to get acceptance of hypermodels by patients and physicians we presented the CHIC platform at clinical conferences and developed a questionnaire dealing with the acceptance of hypermodels.

There are major points that could be extracted from the discussions on the conferences and the questionnaire that will help to increase the acceptance of hypermodels. The way the hypermodels were presented dealt with the fact that these models will be used as decision support services for clinicians to help them to find the best diagnosis and treatment for their patients. Most important in the process of finding reasons that would increase the acceptance rate of hypermodels were the **open discussions with different stakeholders at the conferences**, when the paradigm of the nephroblastoma hypermodel was presented. An important finding was that patients would not accept the use of hypermodels if physicians would not accept hypermodels in their daily practice. The higher the trust of the physician, who is an expert in using hypermodels, in the predictions of the latter is, the more likely the patient will trust hypermodels. This has also been clearly shown by the answers of the questionnaire.

For both groups (patients and physicians) three important points are mandatory for getting acceptance of hypermodels:

1. Clinical relevance of hypermodels
2. Education and explanation of hypermodels in order for the users to better understand them
3. Validation and certification of hypermodels

Clinical relevance of hypermodels is seen as an important issue. Especially clinicians want to deal with hypermodels only, if they can help them to solve relevant clinical questions. The term “relevant” means to them to obtain answers to questions they cannot answer with their current knowledge, because of the complexity of the question or the need for using too many heterogeneous and individual data including genomic information. As hypermodels are complex and difficult to understand, no clinician will use them for simple questions that they can answer rapidly by themselves.

Depending on the stakeholders the explanation of and the education on hypermodels need to be different. Basic scientists want to receive more feedback on how hypermodels are producing a result, whereas clinicians want to know on what data the result of the hypermodel is based and how the hypermodels can be validated, so that they can trust the predictions. Clinicians would never use the prediction of a hypermodel in an individual patient, if there is no guarantee that the result is meaningful and not harming patients.

Validation and certification is regarded as the most important issue in view of hypermodels acceptance. Most of the time devoted to discussions with stakeholders at the conferences was spent on the issues of validation and certification. Basic scientists want to have a guarantee that the models will deliver correct results only depending on the individual data of a patient and that the system is running smoothly.

The most important and interesting point on how to validate a hypermodel was discussed intensively with different stakeholders at the conferences. As a result it was suggested that hypermodels should be regarded like drugs going through different clinical trial phases before they will be approved for market. These four phases in drug development could be applied to hypermodels as well.

During **phase I** one needs to show the scientific correctness of the hypermodel, showing accuracy, security, reliability and other features that are defined by the ISO (International Organization for Standardization, http://www.iso.org/iso/home.html) SQuaRE (Software product Quality

Requirements and Evaluation) and its standards (General Guidance: ISO/IEC 25000, Particular Guidance: ISO/IEC 25040 (ISO/IEC 9126-1 and ISO/IEC 14598-1) and Execution: ISO/IEC 25041 (ISO/IEC 14598-6), ISO/IEC 25042 (ISO/IEC 14598-3), ISO/IEC 25043 (ISO/IEC 14598-4).

In **phase II** a comparison between the prediction of the hypermodel and the real result needs to be analysed and the hypermodel should be optimized so that the prediction of the hypermodel will be compliant with the real situation in a patient. If this is achieved the hypermodel can enter a phase III trial.

As in **phase III** trials for drug development one could initiate a randomized trial comparing standard treatment against treatment that is predicted by a hypermodel. Different endpoints of such a trial can be defined, depending on the intention of the hypermodel. A graphical schema of such a phase III trial is given in figure 5.1.

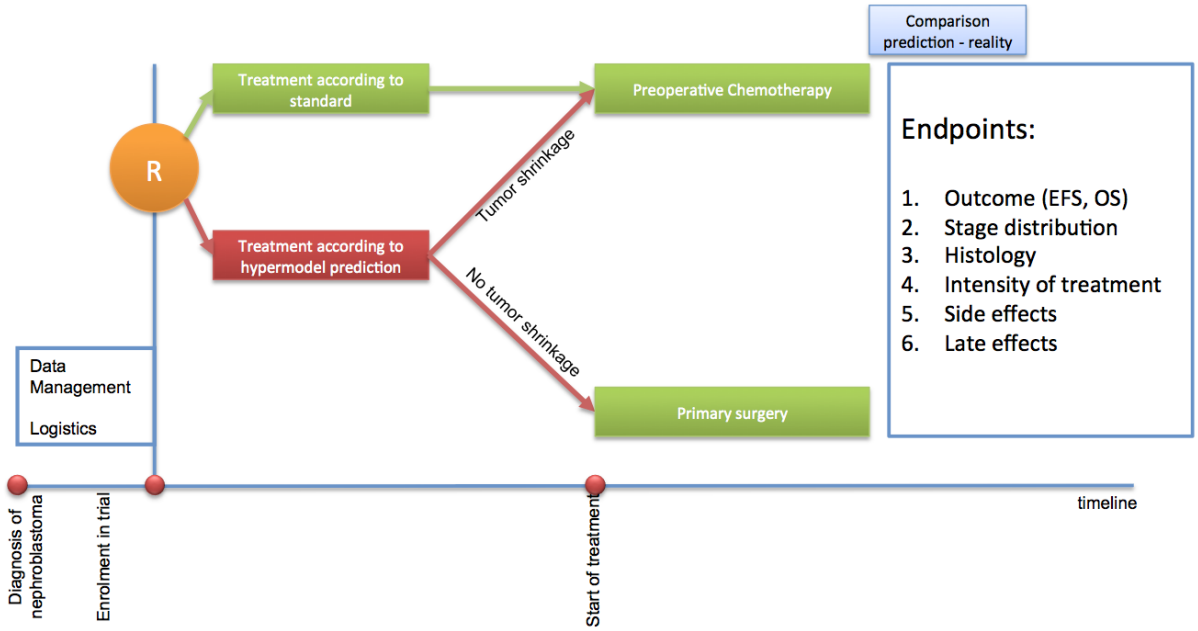

Fig. 5.1: A possible schema for a phase III clinical trial with the usage of a hypermodel.

If such a consecutive follow-up of 'trials' will allow certification of a hypermodel after phase III needs to be discussed with regulatory bodies. But such a way is known to clinicians and would help to accept hypermodels. After a successful phase III trial and having obtained the permission to use the hypermodel in daily clinical care the need for a phase IV is necessary as in drug development. Such a phase would also be able to optimize and fine tune a hypermodel since the more runs of a hypermodel and comparison between prediction and reality, the better the predictions a hypermodel will produce.

Intellectual Property (IP) issues did not play a role for patients and clinicians. Basic scientists only shortly addressed this topic during the open discussions at the conferences. Clinicians just want to know how expensive these hypermodels would be if they are going to the market or if they will be freely available. An answer to this question could not be provided.

Appendix 1 – CHIC questionnaire for the acceptance of hypermodels

Today treatment of diseases is becoming more and more individualized. This is based on the increase of data originating from clinical, laboratory, imaging and research data. Models and hypermodels are developed to analyse these data and gain new knowledge. This knowledge can then be used for decision support by physicians in individual patients.

In order to understand what citizens and patients are thinking about such models/hypermodels the present survey has been developed. It will help to optimize research in this area. A short video will introduce hypermodels for you. It is a hypermodel developed for nephroblastoma, the most common kidney cancer in children. It will answer the question if preoperative chemotherapy will shrink the tumour before surgery. The prediction of this hypermodel may then be used for helping the physician to apply the best treatment for a patient with nephroblastoma.

The video will be followed by a short survey consisting of two parts. The first part is asking demographic questions (7 questions) whereas the second part is related to the understanding of hypermodels (11 questions). Your answers will be anonymous. If you want to get feedback of the results, you need to provide us with an email. This email will not be linked to your answers. The whole survey will take you less than 10 minutes.

-- video presented ---

Part A – Demographic data

1. Country you are living:	……		
2. Age:	…. years		
3. Gender:	male	female	
4. Are you healthy:	yes	no	
If no:	acute	chronic disease	
	Cancer	yes	no
	Please provide your diagnosis: ……..		
5. What is your highest educational degree:		no educational degree	
		Primary school	
		College	
		University	
6. Are you employed:		yes	no
7. Profession:	in healthcare:	yes	no
	in IT sector:	yes	no
	in basic research:	yes	no
	Please provide your profession: ……..		

Part B - Hypermodel specific questions

1. Have you ever heard about hypermodels? yes no

2. After watching the video, do you understand the notion of hypermodels?
yes no

3.Would you allow your physician to use your data for running a hypermodel? yes no

4. Do you trust the prediction of hypermodels? yes no

5. What will increase your trust in hypermodels? ……

6. If your physician would trust in the prediction of the hypermodel, would that help you to better trust more hypermodels? yes
no

7. If your physician is using a hypermodel with your individual data and would like to treat you according to the prediction of the hypermodel, would you like to be treated accordingly?
yes no

if not, why not? ……..

if not, would it be helpful for you to know that other patients were treated successfully according to the prediction of this hypermodel?
yes no

if not, what else needs to be done, so that you would accept to be treated according to the prediction of a hypermodel? ……

8. What can your treating physician do in order for you to increase your trust in the prediction of hypermodels? ……

9. Do you think that in the future hypermodels will be used by physicians? yes no

10. If a hypermodel for your disease would exist, would you try it on your own, to see what the prediction of the hypermodel would be? yes
no

if yes, would you start your treatment according to the prediction? yes no

11. Do you think that demonstrating the run and the prediction of a hypermodel would be helpful in order to explain you your disease and response to treatment?
yes no

Thanks a lot for answering the questions!

The questionnaire can be answered online:

English: http://www.ehealthserver.com/survey/index.php?r=survey/index&sid=423562&lang=en
German: http://www.ehealthserver.com/survey/index.php?r=survey/index&sid=423562&lang=de

The questionnaire is also linked to the CHIC Homepage and distributed via eCancer.