Comparing the quality of therapy-decisions of doctors using personal experience and usual knowledge sources, and doctors using RAMPmedical (a therapy-decision support software for cases involving diabetic patients)

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Introduction

Choosing a therapy for a patient is a complicated task. It is based on many different parameters. The doctor is required to know all possible therapies that are available for the condition of his patient. Using their knowledge and available information the doctors evaluate the treatment which would be most suited to the patient, based on factors such as the stage of the disease, the efficacy needed and the safety of the treatment. This includes taking into account contraindications in regards to the patient's history or current status (blood parameters, comorbidities), as well as possible interactions with other medication the patient is taking at the time [1].

The data relevant to make a therapy decision can be found partly in product characteristics, medical guidelines, and clinical trials. In the European Union there are approximately 30-50 new treatments authorized every year [2,3]. The product characteristics of the 20,000 existing treatments are regularly updated and based on the increased evidence found in case reports. Medical guidelines are being published less often than product characteristics [4]. However, every doctors association has its own guidelines for several conditions [5,6]. Lastly, according to Pubmed, around 30,000 clinical trials are published every year [7]. Each of those sources contains small pieces of a large puzzle that aims to find the optimal therapy for each patient.

It is impossible for any human to keep up with the amount of data being produced. Considering that in Germany every doctor has only 7.5 minutes to spend with their patient, it is inevitable that at some stage an incorrect treatment will be chosen [8]. Alarming statistic from the World Health Organization show that 11% of European Union citizens have been prescribed wrong medication [9].

Wrong treatment doesn't only mean that it will not work. It can be deadly. The Allgemeine Ortskrankenkasse (AOK) has observed that in Germany a patient dies every 30 minutes because they were prescribed the wrong mix of medicine [10]. This high number of fatalities only refers to the deaths relating to contradictory drug interactions. The whole problem is

much bigger, as death due to overseen contraindications or hospitalization due to side-effects is not being taken into account.

RAMPmedical has developed a therapy-decision software to enable doctor to find the best possible therapy for the patient. This is done by taking into account all contraindications, drug-drug interactions and by enhancing the doctors daily workflow. In an easy to see interface it shows the doctor in an easily comparable way the efficacy and the safety of all the therapy adequate for his patient along with other information he needs to have to make his choice, including therapy steps, prices and off-label use. For the moment, it covers diabetes type 2, but we have the ambition to scale it up to all medical fields.

This article explains how we designed a test to verify that our software works.

Methodology

To verify that our software works, we designed 5 cases consisting of patients with diabetes and asked doctors to solve them both with and without our software. We categorized the therapies they chose into three groups: optimal therapy, suboptimal therapy, and dangerous therapy. We also assessed the perceived difficulty of the cases and how confident the doctors were about their choices. To increase our understanding of their daily routine and their concerns, we also added several other questions unrelated to the patient cases.

Patient cases design

The exact patient cases can be found as appendix to this document. Below is a summary of the cases:

- The first case describes a diabetic patient with renal impairment (eGFR of 29) for whom lifestyle intervention is not sufficient.
- The second case describes a diabetic patient who is overweight and hypertensive with a history of lactic acidosis. Currently under lifestyle intervention with insufficient results.
- The third case describes a diabetic patient who is obese with impaired liver function and declining kidney functions (ALT=145, eGFR=28). Currently being successfully treated with metformin.
- The fourth case describes a diabetic patient who is obese, under phenprocoumon medication due to recurrent thrombosis. Currently under lifestyle intervention with insufficient results.
- The fifth case describes a diabetic patient who is overweight and currently under gemfibrozil due to high triglycerides. The patient started metformin but is intolerant to it. The patient wants repaglinide but does not want thiazolidinediones or sulfonylureas.

For each case, the doctor was asked which type 2 diabetes drug or non-drug therapy is the best to treat the patient. And for each therapy decision, doctors were asked how sure they were about their decision. They could answer only using one of the following statements; very sure, sure, neither nor, unsure or very unsure.

Enrollment and allocation of the doctors

The goal was to recruit doctors to answer the patient cases in the form of an online questionnaire. The intention is that that approximately half of them answer to the questionnaire with RAMP (experimental group), the other half without (control group). In order to assess whether RAMP does help doctors a comparison between the outcomes of the experimental and control groups is required.

An initial form was prepared to provide doctors with the ability to register to the testing platform. It contained four questions to identify their seniority level and whether or not they were in contact with diabetics. Doctors could also contact us directly. In such case they were added to the global poll of participating doctors. Once the registrations were complete, the doctors were split into two groups. Those who are in contact with diabetic patients and those who are not.

- Doctors who usually are not in contact with diabetic patients were directly assigned to answer the testing with RAMP, since they do not have the expertise to be able to assess themselves what therapy should be given.
- Doctors who are usually in contact with diabetic patients were randomly assigned to either answering our question with our software, or answering it without our software. To assign those doctors to a category, a binomial distribution with a probability of success of 0.5 was used.

Categorization of the therapies

We categorized the different therapies into 3 groups: optimal therapy, suboptimal therapy, and dangerous therapy.

A therapy was categorized as 'dangerous' when the product characteristics corresponding to this therapy stated that using it in such condition could be dangerous for the patient. Any contraindication due to patients comorbidity, history or other medication lead to a categorization as dangerous. Furthermore, terminating a working treatment without replacing it is also classified as dangerous since glycemia will increase again and endanger the patients health.

A therapy was categorized as 'suboptimal' when it would lead to increased side-effects for the patient, compared to other therapies. That could also include choosing a therapy helping only one of the patient condition, while he has other comorbidity that could be improved together with his diabetes by just one treatment. The reason is that increasing the amount of drug therapy increases the chances of adverse events for the patients.

A therapy was categorized as 'optimal' when it would be among the therapies with lower side-effects and tackling the co-morbidity as well if there are some.

Results

21 doctors participated in the testing. 13 answered using RAMP, and 8 without.

Diversity of the doctors who participated

Among the doctors who were assigned to the group having to answer with RAMP, several did not follow or use the software to answer. In such case, we created another category of doctors that we labeled 'reassigned doctors'. 8 doctors answered without RAMP. 13 answered with, including 5 who were put in the 'reassigned' group because they answered the questionnaire using their personal knowledge and not the RAMP software.

In the control group answering without RAMP, 6 out of 8 doctors were diabetologists / endocrinologists. One a head of clinic, four attending doctors, two residents, and one other.

In the experimental group answering with RAMP, 2 out of 13 doctors were diabetologists / endocrinologists. 5 were general practitioners, and the rest had other specialties such as radiology, OBGYN, or ophthalmology. One was head of a clinic, four were attending doctors, four were residents, and four others. Table 1 summarize the diversity of the participants.

Table 1: Statistics are displayed in percentage by the type of doctors participated to the testing, based on their seniority level and their specialty

General information	Characteristics	Doctors who answered without RAMP (in %)	Doctors who answered with RAMP (in %)
Seniority level	Heads of clinics	12.5	7
	Attending	50	31
	Residents	25	31
	Other	12.5	31
Specialty	Diabetology	75	15
	General medicine / Internal medicine	25	38
	Other	0	47

Categorization of therapies for each patient case

In the case when several answers were provided the answer with the worst possible outcomes was considered for the categorization. For instance, if the answer 'insulin therapy or GLP-1 therapy', GLP-1 considered as 'optimal therapy' and insulin therapy considered as 'suboptimal', the categorization of the answer was 'suboptimal'.

Case One: The right therapies were GLP-1 analogs (Bydureon, Trulicity, Xelevia) or DPP-4 inhibitors (Onglyza). Dangerous therapies were those containing Metformin because they are contraindicated for such renal impairments. Other therapies were suboptimal: Insulin therapy was suboptimal because insulin increases body weight (this patient is already overweight) and in the long term can worsen diabetes. Sulfonylureas were suboptimal because it can often cause hypoglycemic states due to such renal impairments.

Case Two: Dangerous therapies were those containing Metformin. Metformin can trigger lactic acidosis. It is rare but fatal in 50% of cases when it does happen. This means that Metformin is contraindicated in many countries in patients who have a lactic acidosis history. Since the patient is overweight and hypertensive, the right therapies are SGLT-2 inhibitors or GLP-1 analogs. Both drug families improve other comorbidities. The other therapies are 'sub-optimal'. DPP-4 because they do not improve hypertension, sulfonylureas and insulin because it increases weight and does not improve blood pressure.

Case Three: Dangerous therapies were those keeping metformin or withdrawing metformin without trying to reduce blood glucose otherwise. Reason is that metformin is contraindicated for patients with impaired renal values because it increases the risks of fatal lactic acidosis. Sub-optimal therapy are those containing insulin since it would increase the body weight (patient already obese) and therefore worsen diabetes. Right therapies are GLP-1 analogs or DPP-4 inhibitors.

Case Four: The dangerous therapy was metformin because it significantly reduces the efficacy of phenprocoumon and can increase the patients risk of stroke. Because the patient is obese, insulin and sulfonylureas are considered as suboptimal. GLP-1 was considered as the optimal therapy.

Case Five: Repaglinide is a dangerous therapy because it is contraindicated for patients taking gemfibrozil due to significant interactions. Metformin is also considered as dangerous because the patient is intolerant to it. Because of the lipids problems, therapies that are aimed at reducing body weight and diabetes, such as such as SGLT-2 inhibitors or GLP-1 analogs, are the optimal ones. Insulin is suboptimal because it causes weight gain, and DPP-4 is suboptimal to the weight neutrality.

Answers to Patient Cases

The results indicate that doctors who made therapy decisions using RAMP performed significantly better than those who did not:
- 86% were optimal
- 8% were suboptimal
- 6% were dangerous

Doctors who made therapy decisions without using RAMP had a significantly decreased performance result:
- 29% were optimal
- 42% were suboptimal
- 29% were dangerous

The biggest concern was that contraindications and interactions were overlooked, and co-

morbidities were not being taken into consideration by Doctors who did not use RAMP.

Patient Case Outcomes

Figure 1: The Pie-charts breaks down the effectiveness of the therapy decision into three segments; Doctors who answered with RAMP, without RAMP, or those who belonged to the reassigned group. The chart is colour coded. Green indicates an optimal therapy, yellow indicates a suboptimal therapy decision, and red indicated a dangerous therapy decision.
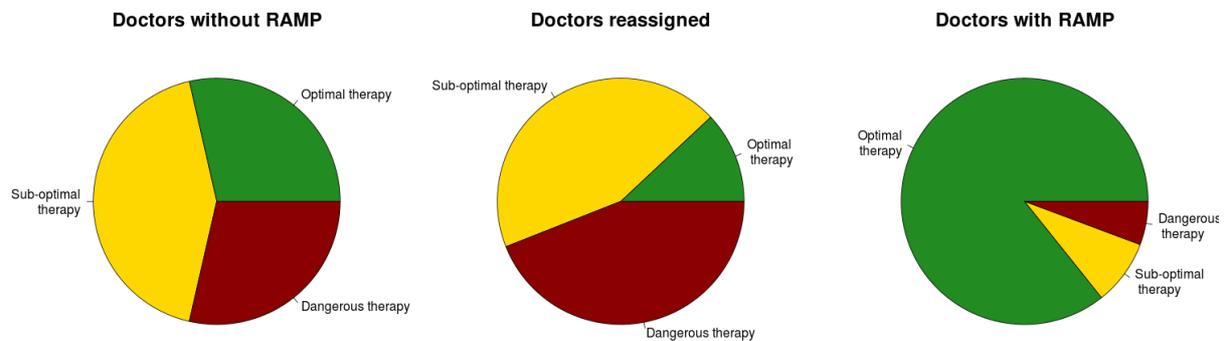
To compare the results of doctors who answered with RAMP and doctors who answered without RAMP, we calculated the significance of the difference between both groups. To assess this, Fisher's 'Exact Test' was applied to the patient case outcomes, to calculate the significance of the difference between adequate therapies and inadequate therapies.

'Optimal' therapies are adequate therapies to prescribe to a patient, while 'dangerous' therapies are inadequate for a patient. To avoid any ambiguity with the 'suboptimal' group of therapies, we performed two series of tests. The first with 'suboptimal' therapies categorized as adequate for a patient, the second with 'suboptimal' therapies categorized as inadequate for a patient.

When 'suboptimal' and 'optimal' therapies were considered to be adequate, and 'dangerous' as inadequate therapies, p-value was calculated to be 0.023. This shows that there is a significant difference in results. The difference is even more significant when only the 'optimal' therapies were considered to be adequate, and the 'suboptimal' and 'dangerous' ones as inadequate therapies. In this case the p-value was below 0.0001.

Those results demonstrate that doctors who answered with RAMP performed significantly better than doctors who answered without, regardless on whether suboptimal therapies were considered as adequate or inadequate for patients.

Doctor's Personal Perception of Cases

Overall, Doctors who answered without RAMP were confident in the therapy decisions they chose for the patient cases (88%).
Doctors who answered with RAMP were less confident with their answer (71%). The results in the table below show a more detailed break-down of doctors perception.

Detailed View of Doctor's perception regarding the cases

Table 2: This table shows how sure doctors were that the therapy they recommended for each patient case was the best available therapy categorized by each group of doctors.

How sure Doctors were about their answer	Cases solved by Doctors without RAMP (%)	Cases solved by Doctors from the reassigned group (%)	Cases solved by Doctors using RAMP (%)
Very sure	48	24	34
Sure	40	52	37
Neither nor	9	4	12
Unsure	3	20	3
Very unsure	0	0	14

The Doctor's Thought the Cases were Easy to Solve

The doctors who solved the patient cases without using RAMP considered them to be easy to solve (76%). Doctors who solved the patient cases using RAMP found the cases more complex and more challenging to analyse. A detailed breakdown of the results is visible below in table 3.

Table 3: This table shows how complex each group of doctors who were either in the group answering without RAMP, with RAMP or were in the reassigned group perceived the cases to be.

Overall difficulty of the cases	For Doctors who did not use RAMP (%)	For Doctors in the reassigned group (%)	For Doctors who used RAMP (%)
Very easy	29	0	14
Easy	57	20	14
Average	14	60	44
Difficult	0	0	14
Very difficult	0	20	14

Discussion

Improvement of decision

Regardless of whether suboptimal decisions were classified as adequate or inadequate therapy, doctors answering using RAMP performed significantly better ($p<0.05$) than doctors answering without. This means that significantly less patients would have been endangered, and significantly more would have an improved quality of life because their diseases would have been better handled.

This proves that RAMPmedical improves the decisions doctors make for patients with type 2 diabetes. This also indicates that the software has the potential to generally improve therapy decisions once it is fully developed and includes more medical fields.

Reassigned group

The group indicates that some doctors did not adhere to use RAMP. The reasons for that were diverse. One Doctor did not have a desktop computer and used a smartphone, however RAMP is not mobile compatible yet. Other doctors were older (>45 years old) and had difficulties using the RAMP UX. This highlights that it will benefit to improve the UI and make it more user-friendly. Lastly, some doctors were not confident about what the software directed them to do and in result chose therapies that they are comfortable with. To solve this, an Artificial Intelligence layer could be added to show doctors examples of what other doctors chose for similar patients.

Errors Made by Doctors using RAMP

Errors still occured by doctors using RAMP. The reason for this was they did not enter all the patient data that was relevant, and therefore we able to choose a therapy that they should not have. These mistakes will not be possible once the software automatically retrieves and inputs the patient data and activates the filter. If it still occurs, to solve this, a layer of Artificial Intelligence could be added to advise the doctor to ask the patient about other specific drugs they are are taking or the medical history the patient has before the therapy is prescribed.

Limitations of the study

The study has been done with 21 doctors, which represents 105 solved patient cases so. The outcomes were diverse and statistically significant. By gathering more evidence it will strengthen the proof that RAMP works.

Furthermore, the patient cases were theoretical. This allowed to normalize the questions and the outcomes of therapy decisions, but they are not a proof that RAMPmedical improves doctors quality of decisions. In order to prove that, pilot studies have to be put in place with several hospitals and a comparison between quality of care before and after the pilot will be required to be carried out.

Conclusion

By designing five cases of patients with diabetes and asking medical doctors which therapy they thought would be the best, assisted both with and without our software, we can show that RAMP has the potential to significantly improve the therapy decisions of doctors. The results of our test also highlight that doctors have the potential to make choices that are more dangerous than they themselves realise. This emphasize the need to increase awareness surrounding this problem. RAMP holds the key to be a game changer in medical practice, and we are doing everything in our power to do so.

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Appendix

Case 1

A 50-year old male has type 2 diabetes. He has tried lifestyle intervention (courses on sport and nutrition, setting up goals on both amount of calories and physical activity) but it did not improve his HbA1C levels enough: they only decreased by 0.3. He is slightly overweight with a BMI of 26. His last blood values showed HbA1C values of 7.8%. His kidneys health has been deteriorating recently and he has an eGFR of 29 mL/min/1.73 m2. He is often in pain and treats it using paracetamol. Liver and heart functions are within normal range.

Blood values:
- HbA1C : 7.8%
- eGFR: 29 mL/min/1.73 m2
- ALT: 18 IU/L

Case 2

A 60-year old female has type 2 diabetes. During the last 3 months, she followed a lifestyle intervention: less daily calories intake and increased physical activity. It lowered her HbA1C by 0.8%, but she still has HbA1C values of 8.3%. She has a BMI of 28 and the clinical state of her liver is normal. She suffers from hypertension. She uses aspirin twice a month if she experiences pain, which are usually headaches. Her kidneys are mildly impaired because she has a eGFR of 75 mL/min/1.73 m2. Furthermore, she had lactic acidosis one year ago, which was resolved with hemofiltration.

Blood values:
- HbA1C : 8.3%
- eGFR: 75 mL/min/1.73 m2
- ALT: 15 IU/L

Case 3

A 55-year old male has type 2 diabetes since over 5 years. He takes 1000 mg metformin daily and follows properly his lifestyle intervention: He has significantly reduced his amount of daily calories intake, and increased his physical activity. So far his HbA1C targets are so far achieved. His body weight has reduced but he is still obese (BMI = 30). His kidney function is declining and is now at 28 mL/min/1.73 m2. Furthermore, his liver function is also impaired with ALT of 145 IU/L. His AST/ALT ratio is 3.5.

Blood values:
- HbA1C : 6.8%
- eGFR: 28 mL/min/1.73 m2
- ALT: 145 IU/L
- AST/ALT: 3.5

Case 4

A 50-year old male was recently diagnosed with type 2 diabetes. During the last 3 months, he followed a lifestyle intervention. This included lower daily calories intake and increased

physical activity. It lowered his HbA1C by 0.4%, but he still has HbA1C values of 7.9%. He is obese and has a BMI of 31. A few years ago, he had venous thrombosis in the right leg, and started taking phenprocoumon. A couple of months ago, he stopped it for a few weeks and the thrombosis reoccurred. That is why he is taking phenprocoumon again. Aside from that he does not usually take other medications except for paracetamol occasionally.

Blood values:
- HbA1C : 7.9%
- eGFR: 95 mL/min/1.73 m2
- ALT: 31 IU/L

Case 5
A 40-year old female has type 2 diabetes. During the last 4 months, she followed courses on nutrition and the importance of physical activity for diabetics. She increased her physical activity and lowered her daily calories intake. It lowered her HbA1C by 0.4%, but she still has HbA1C values of 8.2%. She is overweight and has a BMI of 27. She started with metformin two weeks ago but she is subject to too many side effects (vomiting, diarrhea, nausea, abdominal bloating) and wants to change her therapy. She has several relatives with diabetes and they gave her information about other therapies. She does not want Thiazolidinediones because she heard it increases the risk of cancer. She also does not want Sulfonylureas because someone in her family had bad reaction to it. She insists on getting Repaglinide because, according to her relatives, this is the best working one. She uses paracetamol for occasional pain (twice a week). She also has high triglycerides and uses Gemfibrozil to reduce it.

Blood values:
- HbA1C : 8.2%
- eGFR: 75 mL/min/1.73 m2
- ALT: 22 IU/L