Health Academy
Radboudumc

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| Examination | : | **B2RQ8 Research Personalized healthcare** |
| Date | : | June 29th 2018 |
| Start | : | 13:00 h |

**After finishing the exam, you can take this examination set along with you.**
Please hand in the OTHER part (the answering form) to the supervisor.

**Your are allowed to use a calculator of the type Casio FX-82MS.**

**The questions must be answered in English. If you cannot remember a specific English term, you can use the Dutch term.**

During the exam you have access on a computer to these books:

- Baynes & Dominiczak: Medical Biochemistry
- Campbell: Statistics at square one
- Donders: Literature Measurement errors
- Fletcher: Clinical Epidemiology
- van Oosterom en Oostendorp: Medische Fysica
- Petrie and Sabin: Medical Statistics at a Glance
- Turnpenny: Emery's Elements of Medical Genetics
- Casarett & Doull's Essentials of Toxicology

GENERAL INSTRUCTIONS:

- Below you will find 23 questions on the topics that were covered during Q8 *Research in personalized healthcare*. You can earn a total of 38 points. The number of points awarded per correct answer are indicated at each question. Explain your answers and be concise.
- The available time is **2** hours.
- You are allowed to use scrap paper that will be handed out. Do not use the scrap paper for your answers and do not hand it over to the supervisor.
- Check if your examination set is complete.
- Please write *your name and student number* on each page of the answering form.
- Write your answers on the answering form in the open space below the questions. Read the questions carefully before phrasing your answers.
- Be concise and complete in your answers.
- If necessary you can also use the *backside* of the pages.
- Refrain from using abbreviations in your answers, and write legibly (illegible answers are considered incorrect).
- Please do not use a pencil.
- The use of audiovisual and technical devices is not allowed, unless it is mentioned explicitly elsewhere on this page. Any inappropriate use of such equipment is regarded as fraud.
- Except for the exam forms, some loose writing material and your student card, your table should be empty. No boxes or cases are allowed.
- **After finishing the exam, please hand the answering form to the supervisor. If you have comments about the questions we refer you to the hyperlink of the digital comment form that is included in your "studenten webdossier" below "toetsen".**

SUCCESS

**ATTENTION !!**

**FIRST PUT YOUR NAME AND STUDENT NUMBER ON EVERY PAGE OF THE ANSWERING FORM!**

Name:.....
Student Number:.....

## Instructions

Below you will find 23 questions on the topics that were covered during Q8 *Research in personalized healthcare*. You can earn a total of 38 points. The number of points awarded per correct answer are indicated at each question. Explain your answers and be concise.

Please fill in your name and student number at the top of every answer sheet.

## Personalized Healthcare at Radboudumc

**Personalized Healthcare**

*www.radboudumc.nl/research*

Our frame of reference is always the individual patient, who is unique. Unique characteristics include not only the genetics, biology and physiology, but also the psyche, social environment and wishes, responsibility and capabilities of the individual. In the vision of Radboudumc, all patients participate in their own healthcare. Clinicians, researchers and patients work together to uncover the causes of diseases and find cures for them. In this way, participatory healthcare has become the focal point of patient care, education and research at Radboudumc.

1. The U.S. Food and Drug Administration (FDA) issued a white paper in 2013 where they stated an important change in their perspective on the meaning of "personalized medicine". First personalized medicine was about offering the right drug to the right patient at the right time. Which two important aspects were added to the definition? [2 points]

2. You have collected data on a cohort of patients with small cell lung cancer. They were all treated with R-CHOP chemotherapy (Rituximab, Cyclophosphamide, Hydroxydaunomycin, Oncovin, and Prednisone). Prior to start of therapy all patients underwent a bronchi-alveolar lavage from which tumor cells were isolated. After five years, 53% of the patients are still alive. In a few sentences, describe a study in which you use these samples and data to create a personalized therapy for the treatment of small cell lung cancer. [2 points]

3. Traditional randomized trials are used to evaluate if a treatment works on average. To really tell if a treatment is effective in an individual patient, an N-of-one trial would be preferable if possible. What are the three design features needed in an N-of-one trial? Fill in the blanks: [2 points]

   *In order to perform a N-of-one trial, you need a .....*
   *to test two or more treatments, a ..... measure such as a biomarker or PROM.*

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## Personalized Healthcare in Infectious Diseases and Global Health

The next questions are about the abstract of the article by Mimiaga *et al.* 2017.

**A Pilot Randomized Controlled Trial of an Integrated In-person and Mobile Phone Delivered Counseling and Text Messaging Intervention to Reduce HIV Transmission Risk among Male Sex Workers in Chennai, India.**

*Mimiaga MJ, Thomas B, Biello K, Johnson BE, Swaminathan S, Navakodi P, Balaguru S, Dhanalakshmi A, Closson EF, Menon S, O'Cleirigh C, Mayer KH, Safren SA.*

AIDS Behav (2017) 21:3172–3181

Men who have sex with men (MSM) are at increased risk for HIV infection in India, particularly those who engage in transactional sex with other men (i.e., male sex workers; MSW). Despite the need, HIV prevention efforts for Indian MSW are lacking. As in other settings, MSW in India increasingly rely on the use of mobile phones for sex work solicitation. Integrating mobile phone technology into an HIV prevention intervention for Indian MSW may mitigate some of the challenges associated with face-to face approaches, such as implementation, lack of anonymity, and time consumption, while at the same time proving to be both feasible and useful. This is a pilot randomized controlled trial to examine participant acceptability, feasibility of study procedures, and preliminary efficacy for reducing sexual risk for HIV. MSW (N = 100) were equally randomized to: (1) a behavioral HIV prevention intervention integrating in-person and mobile phone delivered HIV risk reduction counseling, and daily, personalized text or voice messages as motivating "cognitive restructuring" cues for reducing condomless anal sex (CAS); or (2) a standard of care (SOC) comparison condition. Both groups received HIV counseling and testing at baseline and 6-months, and completed ACASI-based, behavioral and psychosocial assessments at baseline, 3, and 6 months. Mixed-effects regression procedures specifying a Poisson distribution and log link with a random intercept and slope for month of follow-up was estimated to assess the intervention effect on the primary outcomes: (1) CAS acts with male clients who paid them for sex, and (2) CAS acts with male non-paying sexual partners-both outcomes assessed over the past month. The intervention was both feasible (98% retention at 6-months) and acceptable (>96% of all intervention sessions attended); all intervention participants rated the intervention as "acceptable" or "very acceptable." A reduction in the reported number of CAS acts with male clients who paid them for sex in the past month was seen in both study conditions. MSW in the intervention condition reported a faster rate of decline in the number of CAS acts with male clients in the past month from the baseline to both the 3-month (B = -1.20; 95% CI -1.68, -0.73; $p < 0.0001$) and 6-month (B = -2.44; 95% CI -3.35, -1.53; $p < 0.00001$) assessment visits compared to the SOC condition. Post-hoc contrasts indicated that, at 3 months, participants in the intervention condition reported 1.43 (SD = 0.29) CAS acts with male clients in the past month compared to 4.85 (SD = 0.87) in the control condition ($p = 0.0003$). Furthermore, at 6 months, the intervention condition participants reported 0.24 (SD = 0.09) CAS acts with male clients in the past month compared to 2.79 (SD = 0.79) in the control condition ($p < 0.0001$). Findings are encouraging and provide evidence of feasibility and acceptability, and demonstrate initial efficacy (for reducing sexual risk for HIV) of a behavioral HIV prevention intervention for Indian MSW that combines daily, personalized text or voice messages with mobile phone-delivered sexual risk reduction counseling and skills building. Future testing of the intervention in a fully powered randomized controlled efficacy trial is warranted.

4. List 4 key elements to HIV care, starting from people at risk to the final stages of the disease.[max 2 points, ½ point per correct item]

5. Patients infected with HIV present in various ways and the progression of the disease shows a high degree of variability between individuals. For instance, some but not all patients are prone to develop cardiovascular disease due to HIV infection. List 2 risk factors that increase the risk of developing cardiovascular disease specific to HIV-infected patients. [max 1 point, ½ point per correct item]

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6. The paper by Mimiaga *et al.* describes a randomized controlled trial aimed to reduce HIV transmission among male sex workers.
    a. Describe the intervention under study. [½ point]
    b. Describe the outcome measure that is studied. [½ point]

7. List three factors that were measured and reported in the study that may cause variation in outcomes when the intervention is put into practice. [max 1 point, ⅓ point per correct item]

8. The study described in the abstract by Mimiaga *et al.* was conducted in India. List three possible barriers to successful implementation of the intervention nationwide in India. [max 3 points, 1 point per correct item]

## Personalized Healthcare Research in Renal Disorders

The next set of questions is about the abstract by Chang *et al.* 2017

**Pharmacogenomic Variants May Influence the Urinary Excretion of Novel Kidney Injury Biomarkers in Patients Receiving Cisplatin**

Cara Chang et al.

*Int. J. Mol. Sci. 2017, 18, 1333; doi:10.3390/ijms18071333*

Nephrotoxicity is a dose limiting side effect associated with the use of cisplatin in the treatment of solid tumors. The degree of nephrotoxicity is dictated by the selective accumulation of cisplatin in renal tubule cells due to: (1) uptake by organic cation transporter 2 (OCT2) and copper transporter 1 (CTR1); (2) metabolism by glutathione S-transferases (GSTs) and –glutamyltransferase 1 (GGT1); and (3) efflux by multidrug resistance-associated protein 2 (MRP2) and multidrug and toxin extrusion protein 1 (MATE1). The purpose of this study was to determine the significance of single nucleotide polymorphisms that regulate the expression and function of transporters and metabolism genes implicated in development of acute kidney injury (AKI) in cisplatin treated patients. Changes in the kidney function were assessed using novel urinary protein biomarkers and traditional markers. Genotyping was conducted by the QuantStudio 12K Flex Real-Time PCR System using a custom open array chip with metabolism, transport, and transcription factor polymorphisms of interest to cisplatin disposition and toxicity. Traditional and novel biomarker assays for kidney toxicity were assessed for differences according to genotype by ANOVA. Allele and genotype frequencies were determined based on Caucasian population frequencies. The polymorphisms rs596881 (SLC22A2/OCT2), and rs12686377 and rs7851395 (SLC31A1/CTR1) were associated with renoprotection and maintenance of estimated glomerular filtration rate (eGFR). Polymorphisms in SLC22A2/OCT2, SLC31A1/CTRI, SLC47A1/MATE1, ABCC2/MRP2, and GSTP1 were significantly associated with increases in the urinary excretion of novel AKI biomarkers: KIM-1, TFF3, MCP1, NGAL, clusterin, cystatin C and calbindin. Knowledge concerning which genotypes in drug transporters are associated with cisplatin-induced nephrotoxicity may help to identify at-risk patients and initiate strategies, such as using lower or fractionated cisplatin doses or avoiding cisplatin altogether, in order to prevent AKI.

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9. According to the abstract above, the polymorphism rs596881 in the gene *SLC22A2* encoding OCT2 is associated with renoprotection in patients treated with cisplatin. Is the polymorphism likely leading to an increased or decreased OCT2 function? [1 point]

10. Why are the proximal tubular epithelial cell susceptible to toxicity from drugs such as cisplatin? [2 points]

11. Researchers used the OCT2 substrate cimetidine as a co-treatment during cisplatin therapy to reduce toxic potential. The co-treatment was not effective as cimetidine inhibited MATE1 with high affinity. Explain in maximum two sentences why MATE1 inhibition still resulted in kidney injury. [1 point]

12. Using the knowledge that OCT2 and MATE1 are involved in renal elimination of cisplatin, which kind of target could be alternatively used to reduce cisplatin toxicity? Please explain. [1 points]

13. To study the interplay of OCT2 and MATE1 in renal cisplatin clearance, the application of a kidney-on-a-chip could be assessed, as this allows polarized culturing of cells under fluidic conditions. To study pharmacogenetic variants as described in the abstract, cells cultured in the system should be genetically characterized. Ideally, you like to include many different variants that allow risk assessment studies prior to the cisplatin treatment. Provide three possible sources or methods that would result in cells containing multiple described variants. [ max 3 points, 1 point per correct answer]

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## Personalized Healthcare Research in Alzheimer's Disease and Stress Related Disorders

The next set of questions is about the abstract by Golde *et al.* 2016.

**Overcoming translational barriers impeding development of Alzheimer's disease modifying therapies.**

J Neurochem. 2016;139 Suppl 2:224-236.

It has now been ~ 30 years since the Alzheimer's disease (AD) research entered what may be termed the 'molecular era' that began with the identification of the amyloid β protein (Aβ) as the primary component of amyloid within senile plaques and cerebrovascular amyloid and the microtubule-associated protein tau as the primary component of neurofibrillary tangles in the AD brain. These pivotal discoveries and the subsequent genetic, pathological, and modeling studies supporting pivotal roles for tau and Aβ aggregation and accumulation have provided firm rationale for a new generation of AD therapies designed not to just provide symptomatic benefit, but as disease modifying agents that would slow or even reverse the disease course. Indeed, over the last 20 years numerous therapeutic strategies for disease modification have emerged, been preclinically validated, and advanced through various stages of clinical testing. Unfortunately, no therapy has yet to show significant clinical disease modification. In this review, I describe 10 translational barriers to successful disease modification, highlight current efforts addressing some of these barriers, and discuss how the field could focus future efforts to overcome barriers that are not major foci of current research efforts. Seminal discoveries made over the past 25 years have provided firm rationale for a new generation of Alzheimer's disease (AD) therapies designed as disease modifying agents that would slow or even reverse the disease course. Unfortunately, no therapy has yet to show significant clinical disease modification. In this review, I describe 10 translational barriers to successful AD disease modification, highlight current efforts addressing some of these barriers, and discuss how the field could focus future efforts to overcome these barriers.

14. List three of the ten translational barriers that help to explain why the basic science knowledge on Alzheimer's disease (AD) has not yet resulted in effective drugs for disease modifying AD treatment. [max 1 point, ⅓ point per correct item]

15. Fill out the pathological structures that can be observed under the microscope that can be observed when studying respectively Abeta and Tau aggregate in Alzheimer dementia? [max 1 point, ½ point per correct answer]

    *The structures that can be seen when Abeta aggregates are*
    .....

    *The structures that can be seen when Tau aggregates are*
    .....

16. The current state of the art in Alzheimer's dementia research is focused on neurochemistry and biocellular research. Thus far this research has not found its way to a clinical application. What three elements would need to be added to enable the development of a personalized intervention for Alzheimer's dementia? [max 1 point, ⅓ point per correct item]

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17. ApoE4 alleles are predictive for a higher chance of beta-amyloid aggregation in the brain. However, we also find amyloid positive PET scans in many older patients without dementia. Current dementia guidelines do not recommend to test for ApoE4 in patients who visit a memory clinic for having their memory complaints diagnosed. However, in some cases genetic testing may be warranted. How can ApoE4 genetic testing be personalized? [3 points]

18. Current evidence suggests that 35% of the prevalent dementia cases in populations can be attributed to modifiable risk factors during their life time. What patient related questions need to be answered to translate this evidence to a personalized management plan for the following patient? Mrs A, aged 78 years, with mild cognitive impairment, to prevent or slow down her cognitive decline because of her preclinical neurodegenerative disease.[2 points]

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## Personalized Healthcare Research with Nanomedicine

The next set of questions is about the abstract by Mitsunaga *et al* 2011.

**Cancer cell-selective in vivo near infrared photoimmunotherapy targeting specific membrane molecules.**

Nature Medicine 2011;17(12): 1685-91.

Three major modes of cancer therapy (surgery, radiation and chemotherapy) are the mainstay of modern oncologic therapy. To minimize the side effects of these therapies, molecular-targeted cancer therapies, including armed antibody therapy, have been developed with limited success. In this study, we have developed a new type of molecular-targeted cancer therapy, photoimmunotherapy (PIT), that uses a target-specific photosensitizer based on a near-infrared (NIR) phthalocyanine dye, IR700, conjugated to monoclonal antibodies (mAbs) targeting epidermal growth factor receptors. Cell death was induced immediately after irradiating mAb-IR700-bound target cells with NIR light. We observed in vivo tumor shrinkage after irradiation with NIR light in target cells expressing the epidermal growth factor receptor. The mAb-IR700 conjugates were most effective when bound to the cell membrane and produced no phototoxicity when not bound, suggesting a different mechanism for PIT as compared to conventional photodynamic therapies. Target-selective PIT enables treatment of cancer based on mAb binding to the cell membrane.

19. Mitsunaga *et al.* contributed to the development of an antitumor photodynamic therapy. Explain why their approach can be termed 'theranostic'.[1 point]

20. What is currently the biggest problem faced in conventional photodynamic therapies? [1 point]

21. List the three main improvements to photoimmunotherapy presented in this study.[1 point per correct answer, max 3 points]

22. Still, the photoimmunotherapy strategy cannot be used to treat all cancers. Mention the two most important prerequisites that have to be fulfilled before a photoimmunotherapy may be developed. Briefly motivate your answer.[1 point per correct answer, 2 points total]

23. Give an example of another payloads to conjugate to the anti-tumor antibody that would serve in anticancer therapeutics? Briefly describe in general terms the working mechanism of this nanoprobe.[1 point]