AMR Diagnostics: Are We Really Missing the Right Assays?
Q+A Responses

Questions	Responses
In my experience, I have not had trouble coming to a consensus with other clinical colleagues on the value of rapid molecular diagnostics for BSI (and potentially other disease states as well). Where it has been challenging is getting the C-suite to recognize this value. Increasingly, lab is being viewed as a cost center and asked to reduce "cost per test". However, sometimes, switching to a cheaper test sometimes leads to less value, less impact on patient outcomes despite reducing overall lab costs. I would like to ask the panelists: a.) what data points or patient outcomes do you believe resonate the most with C-suite, and b.) if we were to design studies to show impact of rapid diagnostics on patient outcomes, what data points do you suggest need to be included in order to get the attention of the C-suite?	Dr. Egli: This is an important point and I feel the same heat in my center. Diagnostics is seen as a cost factor. However, I think it is also our task to provide diagnostic stewardship in the sense of which test for which situation. For this we need evidence not eminence. There are some studies specifically addressing the cost efficacy. In Switzerland for example ICU days are extremely expensive and as we have a per case reimbursement via the health insurance company, every day saved at the ICU is very good for the hospital. So for endpoints I would do - time to optimal therapy (this can easy be shown) also with low patients (and it is a continues outcome e.g. in terms of less hours) and then ICU admission rates is also a good endpoint. There are multiple studies from the US for cost efficacy of panel PCRs in BSI. Dr. Yamshchikov: For us, it has been helpful to look at drug acquisition costs – combination broad spectrum therapy can be more expensive than narrow spectrum single agents, and de-escalation to oral alternatives is even more attractive. The pharmacy is it's own cost center. If we are looking at de-escalation from vancomycin – there are drug levels that need to drawn and run => so nursing time and expense associated with TDM testing is a metric to consider. Another metric to think about is length of stay overall,

	and agree ICU transfer is another consideration. Sometimes patient centered outcomes can be helpful in getting more definition to your data – or at least a different way to look at it.
Regarding the red question mark in 'Opportunity #1': In your clinical practice, how early can we realistically implement molecular methods during the blood culture stage to skip the 12-24h enrichment window? Are we moving towards direct-from-blood diagnosis? Is AI-driven prediction the key to filling this gap?	Dr. Egli: Direct from blood is a dream. The pathogen loads are very low (0.1-10 CFU/mL) - so this is a massive challenge - here I believe that enrichment with microfluid could help. At this stage I rather see the panel PCR and culture work complimentary. Also the presence/abscence of a gene does not give you a MIC. AI-driven prediction could maybe be an option, but again you need large datasets and then there will geography/center specific aspects - e.g. Epic once had an algorithm to flag sepsis - this was an “epic” fail. See the respective NEJM AI paper. Dr. Yamshchikov: I also agree we are very far away from using whole blood RMAs reliably, as I presented. It would lead to tremendous gains though, and we should not lose sight of these on the research agenda. In the interim, potentially some rapid enrichment steps (but again, the trouble with a culture based method remains an issue in low resource settings) or a boosted amplification step, I

	know there are some explorations happening along both of these fronts. I also think some machine-learning based predictions can be instrumental in bridging the gap between data and the point of prescribing – at least in high income countries, where data is available. While the Epic AI prediction algorithm was a massive fail, all four of the INSPIRE trials that used CART (Classification and Regression Tree) machine learning to train a prediction model were a resounding success for antimicrobial stewardship, providing solid and timely decision support at the point of empiric antibiotic selection.
With Total Laboratory Automation (TLA), how much faster can we expect to deliver a definitive AST report compared to manual processing? Are we reaching a 24-hour turnaround for most blood cultures?	Dr. Egli: I did a series of interviews with labs from the US as preparation for a talk - most labs say that due to automated processing and earlier readings they gained especially for negative sample detection in urine culture between 12h-18h. With AST reporting there is to my knowledge no lab which does this automated AST reporting e.g. at night. I am also not aware of a study showing this impact. Dr. Yamshchikov: Agree – urine cultures have had a big change in TAT. For blood cultures, molecular testing is still usually run in batches, usually on day shift. Total Lab Automation is still sometimes less total than advertised for particular assays.
Regarding the single-cell AST via microfluidics: Do you believe that AI	Dr. Egli: Yes. There are also some startups which go in this direct. For ID of species

computer vision will eventually replace manual optical density measurements globally, especially in resource-limited settings?	based on movement patterns of bacteria - see PhAST. But I am sure there are also other companies. Dr. Yamshchikov: I agree, AI could certainly be used to assess and interpret the single cell tubes or plates, using a cell phone or another camera. However that still leaves us with the real world challenges of getting the physical set up to do microfluidics available in more remote or resource limited settings
How would you explain such a high proportion of Klebsiella pneumoniae shown on slide 26?	Dr. Egli: I do not have an explanation for this. In my center clearly E. coli would be first, then followed by S. aureus and K. pneumoniae. Could be a specific cohort aspect. This is what I mean with the fact that there are different cohort effects which need to be considered. Dr. Yamshchikov: Yes that is interesting – must be some local flavor…