Medicom International Conference Series in Urology

# 2021 Genitourinary Cancers Symposium

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PEER-REVIEWED CONFERENCE REPORT


**Apalutamide in prostate cancer**

In the ACIS trial, the addition of apalutamide to abiraterone acetate plus prednisone/prednisolone reduced the risk of radiographic progression or death in men with mCRPC who had not received prior chemotherapy.

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**Superior outcomes with nivolumab + cabozantinib in RCC**

An in-depth analysis of CheckMate 9ER of nivolumab plus cabozantinib versus sunitinib demonstrated superior clinical outcomes and health-related quality of life in patients with renal cell carcinoma.

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**Enfortumab vedotin promosing for bladder cancer**

In the phase 3 EV-301 trial, treatment with enfortumab vedotin resulted in prolonged overall survival rates in patients with previously treated locally advanced or metastatic urothelial carcinoma compared with treatment with chemotherapy.

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Editor Dr Stefan Rauh, Centre Hospitalier Emile Mayrisch, Esch, Luxembourg

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# Letter from the Editor

Dr Stefan Rauh

**Dear Reader,**

I hope you will enjoy our Medicom Conference Report of this year's ASCO GU Symposium. As usual, I'll just sample some abstracts as "teasers":

As you will see, we are coming closer to implementing a personalised medicine approach to prostate cancer, with both new prognostic and predictive markers identified.

LuPSMA has been used in daily practice for years in some European countries – now there's more evidence that this was/is justified.

A new target, a new conjugate – very promising results in advanced bladder cancer treatment.

This comes at a price – and we are increasingly at odds to pay for. Please read the interesting article on the necessary overhaul of licensing and reimbursement of oncology drugs.

So, how about repurposing a cheap drug? Is there a new role for ACE inhibitors in bladder cancer treatments? It may be a little early for that, as this is retrospective data – and there's a long history of supposedly promising but finally inefficient repurposed drugs in oncology. Still..

Please enjoy our congress report.

Yours, sincerely,
Stefan Rauh

**Biography**
Dr Stefan Rauh is currently working as haemato-oncologist in the oncology department of Centre Hospitalier Emile Mayrisch, Esch, Luxembourg. He is mainly involved in clinical work but also in research and teaching activities and is interested in public policy and international cooperation projects in oncology. He is member of the ESMO Practicing Oncologist's Working Group since 2011 (chair 2014–2018), member of the ESMO Public Policy Committee, and has been an ESMO Executive Board member in 2015–2016. He is co-author of the 2017 ESMO European Cancer Patient Coalition (ECPC) Patient Survivorship Guide and an invited expert for the ECPC.

**Conflict of Interest:**
Nothing to declare.

# Prostate Cancer

## Lu177 as a promising new therapy for metastatic prostate cancer

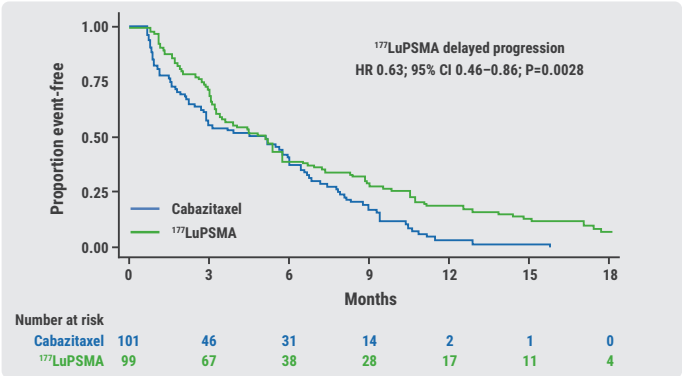
**Radionuclide therapy directed towards prostatespecific membrane antigen (PSMA) showed promising results in men with docetaxel-treated metastatic castration-resistant prostate cancer (mCRPC) [1]. A phase 2 trial comparing the use of radionuclide therapy using lutetium-177 (Lu177) with chemotherapy using cabazitaxel found greater reductions in prostate-specific antigen (PSA) levels, longer periods of progression-free survival (PFS), and greater tumour objective response rates (ORR) in patients treated with Lu177.**

The cell surfaces of prostate cancers strongly express PSMA – even more so in cases of mCRPC. For this reason, PSMA is used both for imaging prostate cancer and as a target for radionuclide therapy.

Dr Michael Hofman (Peter MacCallum Cancer Centre, Australia) discussed the open-label, randomised, multicentre, phase 2 TheraP trial (NCT03392428), which assessed the activity and safety of Lu177-labelled PSMA (LuPSMA) for the treatment of mCRPC [1]. Included men with docetaxel-treated mCRPC and high PSMA expression (n=200) were randomised to receive either ≤6 cycles of radionuclide therapy with LuPSMA or ≤10 cycles of chemotherapy with cabazitaxel.

The primary outcome measure was PSA response rate, defined as the proportion of participants in each group with a ≥50% reduction in PSA from baseline. In the Lu177 group, 65 men (66%) achieved this outcome, compared with 37 men (37%) in the cabazitaxel group (see Figure).

**Figure: Primary outcome measure of progression-free survival [1]**




CI, confidence interval; HR, hazard ratio; $^{177}$LuPSMA, lutetium-177-labelled prostate-specific membrane antigen.

Secondary outcome measures included 9 parameters and were analysed after a median follow-up period of 18.4 months. PFS was 19% (95% CI 12–27%) in the radiotherapy group versus 3% (95% CI 1–9%) in the cabazitaxel group (HR 0.63; 95% CI 0.46–0.86; P=0.003; 173 events). Comparable results were found for both radiographic PFS (HR 0.64; 95% CI 0.46–0.88; P=0.007; 160 events) and PSA-PFS, which was defined as the time from randomisation to PSA progression (HR 0.60; 95% CI 0.44–0.83; P=0.002; 172 events). ORR was 49% (95% CI 33–65%) in the Lu177 group and 24% (95% CI 11–38%) in the chemotherapy group (P=0.019). Overall survival will be monitored for 4 years; this data is not yet available since the study only reached its completion date January 2021. To date, 90 deaths are reported. Regarding pain outcomes, 60% of participants in the radiotherapy arm and 43% of participants in the cabazitaxel arm reported pain (RR 1.42; 95% CI 0.84–4.48; P=0.10) at the end of follow-up.

Adverse events (AEs) were monitored from the time of first study dose to 12 weeks after treatment completion. Fewer grade 3 and 4 AEs occurred in the Lu177 group than in the cabazitaxel group (33% vs 53%). The top 3 grade 3 or 4 AEs experienced in the Lu177 group were thrombocytopenia, anaemia, and fatigue; in the cabazitaxel group, they were neutropenia, anaemia, and diarrhoea.

Concerning health-related quality of life outcomes, global health status scores were similar between the groups: LuPSMA was 64 (95% CI 61–67) versus 60 for cabazitaxel (95% CI 57–64). Nonetheless, the Lu177 group reported favourable outcomes compared with the cabazitaxel group in the domains fatigue (34 vs 40; P<0.05), social functioning (79 vs 73; P<0.05), insomnia (24 vs 29; P<0.05), and diarrhoea (8.3 vs 15.6; P<0.001). No domains were favourable in the chemotherapy group.

Dr Hofman concluded that these interim results support the use of LuPSMA as an alternative to cabazitaxel in men with docetaxel-treated mCRPC.


1. Hofman M. 177Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel: Updated results including progression-free survival (PFS) and patient-reported outcomes (PROs) (TheraP ANZUP 1603). Abstract 6, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

## Role of prostate cancer genomics is evolving

**Compelling preliminary evidence supports the use of genomics to inform clinical decision-making for the management of prostate cancer. A genome-wide RNA array could serve as an independent prognostic predictor of oncological outcomes.**

Dr Ashley Ross (Feinberg School of Medicine, Northwestern University, Chicago, USA) reviewed outcomes of interventions in prostate cancer that considered the Genomic Classifier (GC) score of participants [1]. The Decipher test is a genome-wide RNA expression array that yields a GC score based on 22 genes associated with oncologic pathways. It has been highly validated and is widely available. The GC score ranges from 0–1, with a score of 0–0.45 representing a low risk of clinical progression and a score of 0.60–1.0 representing a high risk of clinical progression.

Dr Ross suggested that the 22-gene GC was an independent prognostic predictor of clinical outcomes following prostatectomy. Dr Ross further demonstrated that adjuvant radiation (defined as radiation administered before reaching a prostate-specific antigen [PSA] value of 0.1 ng/mL) can be considered for patients with >1 of the following risk factors: seminal vesicle invasion, microscopic lymph node involvement, a high Gleason grade group, or a high GC score (i.e. >0.60).

Finally, men who have a low GC score (i.e. <0.45) and receive early salvage radiation should consider the omission of androgen deprivation therapy, as analyses have demonstrated only minimal effect on distant metastases and cancer-specific mortality, and decreased overall survival in these situations. However, in men with intermediate or high GC scores receiving early salvage radiation therapy, all 3 of these parameters were improved.

1. Ross A. Use of Genomics to Guide Treatment Decisions in Post-prostatectomy Patients. ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

## Apalutamide prolongs progression-free survival in prostate cancer

**The addition of apalutamide to abiraterone acetate plus prednisone/prednisolone (AAP) reduced the risk of radiographic progression or death in men with metastatic castration-resistant prostate cancer (mCRPC) who had not received prior chemotherapy [1].**

Both activated androgen receptors and elevated androgen production promote prostate cancer; therefore, treatment is directed towards both blocking androgen receptors and suppressing androgen production. Apalutamide is an androgen receptor inhibitor and abiraterone acetate is an androgen inhibitor that works via ligand suppression. Abiraterone acetate is administered in combination with either prednisone or prednisolone. The ACIS trial (NCT02257736) hypothesised that additional benefit could be conferred by combining these therapies.

Dr Dana Rathkopf (Memorial Sloan Kettering Cancer Center, New York, USA) shared the results of the phase 3, randomised, double-blind ACIS trial designed to compare radiographic progression-free survival (rPFS) in mCRPC patients receiving apalutamide in addition to AAP with rPFS in mCRPC patients with receiving placebo plus AAP. None of the 982 patients in the study had been previously treated with chemotherapy.

The primary endpoint was investigator-assessed rPFS over a time frame defined as time from randomisation until death, loss to follow-up, withdrawal of consent, or end of study, whichever occurred first, up to 5 years. Progression of soft tissue lesions was defined according to the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. After a median follow-up of 25.7 months, the median rPFS in the apalutamide plus AAP group was 22.6 months, versus 16.6 months in the placebo plus AAP group (HR 0.69; 95% CI 0.58–0.83; P<0.0001). These results equated to an extension of rPFS of 6 months and a 31% reduction in risk of rPFS in chemotherapy-naïve mCRPC patients.

Secondary outcomes were overall survival, prostate-specific antigen (PSA) response, time to initiation of opioid use, time to initiation of chemotherapy, and time to pain progression (as measured by the Brief pain inventory-short form scale). The first interim analysis for overall survival also occurred after a median period of 25.7 months, and the apalutamide plus AAP treatment arm showed a longer median OS than the placebo plus AAP treatment arm, although not statistically significant. The apalutamide plus AAP group demonstrated a significantly higher rate of ≥50% decline in PSA compared with placebo plus AAP (RR 1.09; 95% CI 1.02–1.17; P=0.015). Time to PSA response, time to initiation of opioid use, time to initiation of chemotherapy, and time to pain progression did not differ significantly between the 2 treatment groups.

In terms of treatment-emergent adverse events, 310/490 (63.3%) participants in the apalutamide plus AAP group reported grade 3 to 4 adverse events, compared with 275/489 (56.2%) participants in the placebo plus AAP group. No new safety concerns were identified.

1. Rathkopf D. Final results from ACIS, a randomised, placebo-controlled double-blind phase 3 study of apalutamide and abiraterone acetate plus prednisone (AAP) versus AAP in patients with chemo-naive metastatic castration-resistant prostate cancer (mCRPC). Abstract 9, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

## Dose-intensified radiation therapy fails to provide better outcomes in prostate cancer

**A dose-intensified salvage radiotherapy protocol administered to men with adenocarcinoma of the prostate who had undergone radical prostatectomy failed to prolong freedom from biochemical progression of the disease.**

Prof. Pirus Ghadjar (Charité Universitätsmedizin Berlin, Germany) presented the results of the SAKK 09/10 trial (NCT01272050), an open-label, multicentre, randomised phase 3 trial that sought to compare the effectiveness of 2 salvage radiotherapy regimes for the treatment of patients who had relapsing prostate cancer following radical prostatectomy [1]. Relapse was defined as 2 consecutive rises in prostate-specific antigen (PSA) level with the second rising value >0.1 ng/mL, or 3 consecutive rises.

Patients (n=350) were randomised 1:1 to receive either conventional-dose radiotherapy (64 Gray [Gy] in 32 fractions administered over 6.4 weeks) or dose-intensified radiotherapy (70 Gy in 35 fractions administered over 7 weeks) directed to the prostate bed.

The primary endpoint was freedom from biochemical progression (defined as PSA ≥0.4 ng/mL and rising). At 6 years, freedom from biochemical progression was 62.3% versus 61.3% for the 64 Gy versus the 70 Gy arm, respectively, with an HR of 1.14 (95% CI 0.82–1.60; log-rank P=0.44).

Secondary endpoints included clinical progression-free survival, time to hormonal treatment, and overall survival. These outcome measures were not significantly different between the treatment groups.

Genitourinary (GU) and gastrointestinal (GI) toxicity were tracked as well. GU toxicity was not significantly different between the groups; however, the higher-dose protocol was associated with increased GI toxicity.

1. Ghadjar P. Dose-intensified versus conventional dose-salvage radiotherapy for biochemically recurrent prostate cancer after prostatectomy: Six-year outcomes of the SAKK 09/10 randomised phase 3 trial. Abstract 194, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

## Intrinsic tumour biology may be predictive of treatment response in prostate cancer

**Molecular determinants may help to identify patients that will derive the best responses to apalutamide for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC). This was concluded based on data from the biomarker cohort of the phase 3 SPARTAN trial.**

The SPARTAN trial (NCT01946204) was a multicentre, randomised, double-blinded, phase 3 trial investigating apalutamide for the treatment of nmCRPC [1]. Included men (n=1,207) were randomised 1:2 to receive either apalutamide plus androgen deprivation therapy (ADH; n=401) or placebo plus ADH (n=806) until disease progression, withdrawal of consent, unacceptable toxicity, or death. At the primary endpoint analysis presented at ASCO 2020 and published in the *New England Journal of Medicine*, both metastasis-free survival and overall survival were significantly improved in the apalutamide arm [2,3].

Prof. Felix Feng (University of California San Francisco, USA) presented results from his team's analysis of the molecular signatures obtained from the biomarker cohort of the SPARTAN trial (n=233). For this analysis, participants were subdivided into those with early progression (EP) of the disease and those who were long-term responders (LTR). Using archival tissue samples from the biomarker cohort of the SPARTAN trial, researchers aimed to identify molecular signatures associated with either EP or LTR responses to treatment – either by apalutamide (n=60) or placebo (n=37).

Patients with EP or LTR had similar baseline characteristics. Increased immune activity, decreased tumour vascularisation, or decreased proliferative capacity at baseline were associated with LTR in the apalutamide group but not the placebo group (see Table). The inverse was true for EP in the apalutamide group, while increased hormonal independence or metastatic capacity at baseline was associated with EP in the placebo group. Tumours with increased expression of signatures suggestive of T-cell proliferation demonstrated a more favourable response

to apalutamide; this response was true in both basal and luminal tumours.

**Table: Molecular signatures in the apalutamide + ADT group. Based on [1]**

| Signature classification | Transcriptional signatures | Differential expression | | P-value LTR vs EP |
|---|---|---|---|---|
| Immune activity | T-cell stimulation: ICOS | ↑ LTR | ↓ EP | 0.003 |
| | T-cell proliferation: IL-2 signalling | ↑ LTR | ↓ EP | 0.072* |
| | Antigen presentation: TAP2 | ↑ LTR | ↓ EP | 0.025 |
| Tumour vascularisation | Tumour hypoxia | ↓ LTR | ↑ EP | 0.061* |
| | Angiogenesis | ↓ LTR | ↑ EP | 0.038* |
| Proliferative capacity | Prostate tumour proliferation score 1 | ↓ LTR | ↑ EP | 0.053 |
| | Prostate tumour proliferation score 2 | ↓ LTR | ↑ EP | 0.053* |

* Reached nominal statistical significance in Cox regression analysis only.
EP, early progression; ICOS, inducible co-stimulatory; IL, interleukin; LTR, long-term responders; TAP2, transporter associated with processing 2.

Prof. Feng concluded that these molecular signatures may be useful to predict which patients with nmCRPC will derive the most favourable treatment responses to apalutamide and other androgen receptor signal inhibitors.


1. Feng F. Molecular determinants associated with long-term response to apalutamide in nonmetastatic castration-resistant prostate cancer (nmCRPC). Abstract 8, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.
2. Small EJ, et al. Abstract 5516, ASCO Virtual Meeting, 29–31 May 2020.
3. Smith MR, et al. N Engl J Med. 2018; 378: 1408–1418.


## Final TITAN trial results favour use of apalutamide

**Apalutamide plus androgen deprivation therapy (ADT) in men with metastatic castration-sensitive prostate cancer (mCSPC) demonstrated improved overall survival (OS) and reduced risk of death compared with placebo.**

The phase 3, randomised, placebo-controlled, double-blind TITAN trial (NCT02489318) investigated whether the addition of apalutamide to ADT would improve radiographic progression-free survival (rPFS) or OS in men with mCSPC [1]. Of the 1,052 participants, 525 received apalutamide, while 527 received a placebo. Investigators performed their first interim analysis after a median follow-up period of 22.7 months. At that time, both OS and rPFS were significantly better in the apalutamide group (OS, HR=0.67; rPFS, HR=0.48) than in the placebo group.

This analysis coincided with the unblinding of TITAN, giving patients from the placebo arm the opportunity to proceed to the open-label extension phase of the trial. Of the 527 patients in the placebo arm, 208 (39.5%) chose to cross over to receive apalutamide. Dr Kim Chi (British Columbia Cancer and Vancouver Prostate Centre, Canada) presented the TITAN results following the crossover, after nearly 4 years of follow-up.

The crossover group underwent treatment for a median duration of 15.4 months, as compared with a median treatment duration of 39.3 months for the apalutamide group, and 20.2 months for the placebo group as a whole.

Final analyses continue to show superior OS outcomes in the apalutamide group; 48-month survival rates were 65% in the apalutamide group versus 52% in the placebo group. This corresponded to a 35% reduction in the risk of death, which became a 48% reduction of death risk with the inclusion of the crossover patients. Health-related quality of life outcomes did not differ between groups, and the safety profile was consistent with that reported previously. Dr Chi concluded that these final results from TITAN support the use of apalutamide in men with mCSPC.


1. Chi K. Final analysis results from TITAN: A phase III study of apalutamide versus placebo (PBO) in patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC) receiving androgen deprivation therapy (ADT). Abstract 11, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

# Penile Cancer

## Prognosis of penile cancer associated with HPV status

**Determination of human papillomavirus (HPV) status should be done routinely at diagnosis of penile cancer. HPV-positive penile cancer has a much better prognosis than HPV-negative penile cancer, independent of age, stage, comorbidities, or treatment method [1].**

Dr Adithya Chennamadhavuni (University of Iowa, USA) shared the results of his team's analysis of data from the National Cancer Database (NCDB). The analysis focussed on characteristics and outcomes of 486 men who were diagnosed with penile cancer between 2004 and 2016 and who had a known HPV status. Among 486 patients with penile squamous cell cancer, 139 (29%) had tested positive for HPV. These findings are consistent with those of previous studies, which have documented that HPV is present in 30–50% of penile cancers. The majority of participants were white, <65 years old, from low-income areas, and had either public or no insurance coverage. These characteristics were similar in HPV-negative versus HPV-positive patients.

Most HPV-positive patients presented with an early-stage tumour; at time of diagnosis, 77% had a moderately to poorly differentiated tumour. Regardless of treatment modality, a superior 5-year overall survival rate was found among HPV-positive patients: 62% versus 50% in HPV-negative patients. The risk of death in patients who had tested negative for HPV was 1.49 times that of the risk of death in patients who had tested positive for HPV. Multivariable analysis demonstrated that survival rates were superior in patients who were <65 years old, had a low Charlson-Deyo comorbidity index score (0–1), and had been diagnosed at an earlier stage of the disease.

According to Dr Chennamadhavuni, this analysis reinforces that HPV status has a bearing on the prognosis of penile cancer and should therefore be performed routinely at time of diagnosis.

1. Chennamadhavuni A. Prognostic significance of human papilloma virus (HPV) in penile cancer: A National Cancer Database (NCDB) study. Abstract 5, ASCO Genitourinary Cancers Symposium, 11–13 February 2021.

# Renal Cancer

## Superior clinical outcomes and QoL with nivolumab plus cabozantinib in RCC

**Patients with renal cell carcinoma (RCC) treated with nivolumab plus cabozantinib demonstrated both superior clinical outcomes and superior health-related quality of life outcomes compared with patients treated with sunitinib. This was found in an in-depth analysis of the CheckMate 9ER trial.**

The CheckMate 9ER trial (NCT03141177) is a phase 3, open-label, randomised controlled trial investigating whether nivolumab combined with cabozantinib is a safe and effective intervention compared with sunitinib in patients with previously untreated advanced or metastatic RCC [1]. Included patients (n=651) were randomised to nivolumab plus cabozantinib (n=323) or sunitinib (n=328) as first-line therapy until either progression of the cancer or unacceptable toxicity, with a maximum treatment duration of 2 years.

Primary and secondary outcomes were reported previously and published recently, with the primary aim of progression-free survival being superior for nivolumab plus cabozantinib after a median follow-up of 18.1 months (HR 0.51; P<0.0001) [2,3]. Both key secondary outcome measures overall survival (OS) and objective response rate (ORR) were superior in the nivolumab plus cabozantinib group (HR 0.60; OS, P=0.001; ORR, P<0.0001).

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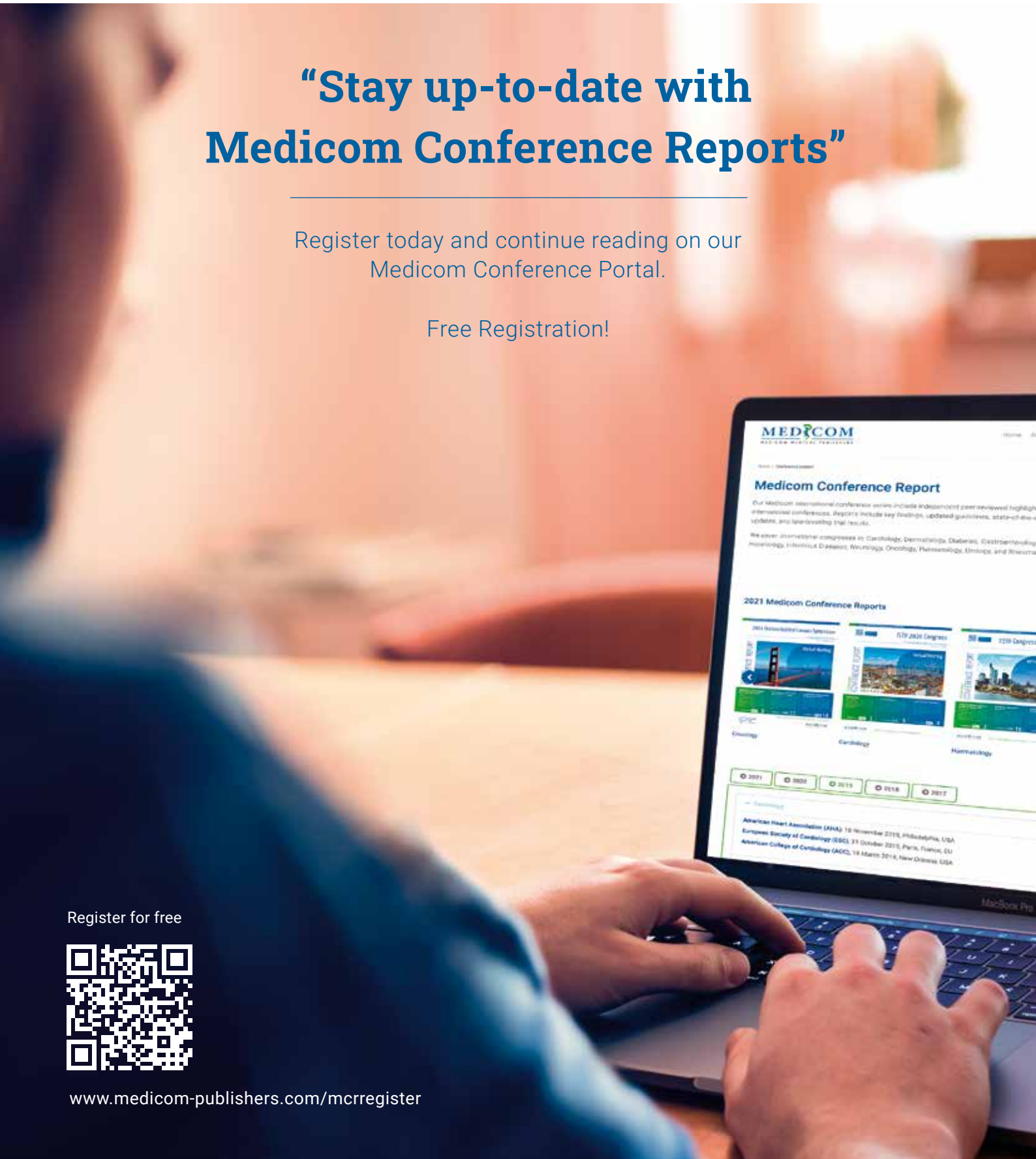


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