2017

Top 10 Articles of the Year
# 1
Nature vs. Nurture
(part 1)
What causes cancer?
Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention

Cristian Tomasetti,¹,²* Lu Li,² Bert Vogelstein³*
Premises

1. All cancers are the result of genetic mutations.

2. Mutations have 3 possible etiologies:
   a. heredity (H)
   b. environmental factors (E)
   c. replicative errors during cell division (R)
On average there are 3 mutations with each cell division in normal tissues.

Each tissue has a specific number of cell divisions during a lifetime.

If these random mutations create drivers for oncogenesis, there should be a correlation between a tissue’s number of lifetime divisions and cancer incidence.
For 69 countries, the correlation between the number of stem cell divisions in 17 different tissues and the lifetime incidence of cancer in those tissues.
If an environmental factor increases the normal somatic mutation rate $X$ fold, then $(X-1)/X$ of the overall mutations can be attributed to that factor.

No significant hereditary factors for lung adenocarcinoma have been identified, so all the risk is due to environment and replicative mutations.
Epidemiology suggests 90% of lung adenocarcinoma is preventable (environmental); applying our formula \((X-1)/X\) we calculate that 35% of the driver mutations are due to replicative errors.
Fig. 3. Etiology of driver gene mutations in women with cancer. For each of 18 representative cancer types, the schematic depicts the proportion of mutations that are inherited, due to environmental factors, or due to errors in DNA replication (i.e., not attributable to either heredity or environment). The sum of these three proportions is 100%. The color codes for hereditary, replicative, and environmental factors are identical and span white (0%) to brightest red (100%). The numerical values used to construct this figure, as well as the values for 14 other cancer types not shown in the figure, are provided in table S6. B, brain; Bl, bladder; Br, breast; C, cervical; CR, colorectal; E, esophagus; HN, head and neck; K, kidney; Li, liver; Lk, leukemia; Lu, lung; M, melanoma; NHL, non-Hodgkin lymphoma; O, ovarian; P, pancreas; S, stomach; Th, thyroid; U, uterus. [Image: The Johns Hopkins University]
What does this mean for the public health approach to cancer in a given country?

For the U.K., with respect to cancer etiology, on average:
- E: 29% of mutations
- H: 5% of mutations
- R: 66% of mutations

Because multiple mutations are required for cancer development, overall 42% of cancers are preventable.
#2
Nature vs. Nurture (part 2)
What causes heart disease?
Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease

Amit V. Khera, M.D., Connor A. Emdin, D.Phil., Isabel Drake, Ph.D., Pradeep Natarajan, M.D., Alexander G. Bick, M.D., Ph.D., Nancy R. Cook, Ph.D., Daniel I. Chasman, Ph.D., Usman Baber, M.D., Roxana Mehran, M.D., Daniel J. Rader, M.D., Valentin Fuster, M.D., Ph.D., Eric Boerwinkle, Ph.D., Olle Melander, M.D., Ph.D., Marju Orho-Melander, Ph.D., Paul M Ridker, M.D., and Sekar Kathiresan, M.D.

Khera AV et al. NEJM 2016
Atherosclerosis Risk in Communities Study (1989)
- 7000 subjects from 4 communities: Jackson MS (African American only); suburban Minneapolis; a NC county, including Winston-Salem; a Maryland county, including Hagerstown

Women’s Genome Health Study (2008)
- 21,000 US female health professionals

Malmo Study
- 22,00 residents of Malmo, Sweden

Biolimage Study
- 6000 residents of Chicago and Fort Lauderdale recruited through Humana Health System

All free of clinically evident coronary artery disease at time of study entry.
Venous blood samples obtained from all participants at study entry.
All completed detailed dietary questionnaires.
End point: composite of MI, coronary revascularization, death from coronary artery disease.
Genetic and Lifestyle Risk Scores

All subject blood samples tested for 50 single-nucleotide polymorphisms associated with coronary artery disease.

- High Risk: top quintile of total SNP scores
- Intermediate Risk: 2nd – 4th quintiles of total SNP scores
- Low Risk: lowest quintile of total SNP scores

All classified by healthy life-style factors: no current smoking; no obesity; physical activity at least once weekly; healthy diet.

- Favorable: 3-4 factors
- Intermediate: 2 factors
- Unfavorable: 0-1 factors
Atherosclerosis Risk in Communities

Genetic Risk

- High: hazard ratio, 1.75 (1.46–2.10)
- Intermediate: hazard ratio, 1.27 (1.09–1.49)
- Low (reference)

Lifestyle Risk

- Unfavorable: hazard ratio, 1.71 (1.47–1.98)
- Intermediate: hazard ratio, 1.18 (1.02–1.36)
- Favorable (reference)

Years of Follow-up

Standardized Coronary Event Rate

Khera AV et al. NEJM 2016
B Women’s Genome Health Study

Genetic Risk

- High: hazard ratio, 1.94 (1.58–2.39)
- Intermediate: hazard ratio, 1.38 (1.14–1.66)
- Low (reference)

Lifestyle Risk

- Unfavorable: hazard ratio, 2.27 (1.92–2.67)
- Intermediate: hazard ratio, 1.32 (1.14–1.53)
- Favorable (reference)

Khera AV et al. NEJM 2016
C Malmö Diet and Cancer Study

Genetic Risk

- High; hazard ratio, 1.98 (1.76–2.23)
- Intermediate; hazard ratio, 1.35 (1.22–1.50)
- Low (reference)

Lifestyle Risk

- Unfavorable; hazard ratio, 1.77 (1.61–1.95)
- Intermediate; hazard ratio, 1.09 (1.00–1.19)
- Favorable (reference)

Khera AV et al. NEJM 2016
Figure 3. 10-Year Coronary Event Rates, According to Lifestyle and Genetic Risk in the Prospective Cohorts.

Shown are standardized 10-year cumulative incidence rates for coronary events in the three prospective cohorts, according to lifestyle and genetic risk. Standardization was performed to cohort-specific population averages for each covariate. The I bars represent 95% confidence intervals.
Figure 4. Coronary-Artery Calcification Score in the BioImage Study, According to Lifestyle and Genetic Risk.

Among the participants in the BioImage Study, a standardized score for coronary-artery calcification was determined by means of linear regression after adjustment for age, sex, education level, and principal components of ancestry. Standardization was performed on the basis of study averages for each covariate. Average standardized coronary-artery calcification scores are expressed in Agatston units, with higher scores indicating an increased burden of coronary atherosclerosis. The I bars represent 95% confidence intervals.
“Aside from slight differences in LDL cholesterol levels and a family history of coronary artery disease, genetic risk was independent of traditionally measured risk factors.”

Khera AV et al. NEJM 2016
#3 Lung Cancer Screening
Why screen for lung cancer?

- relatively high incidence
- high morbidity and mortality
- high risk population easily identified
- early diagnosis correlates with improved outcome

and.....
We now have a “proven” screening tool: Low-Dose CT Scan
## Major LDCT Lung Cancer Screening Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Smoking Hx</th>
<th>Modality</th>
<th>Lung CA mortality</th>
<th>Total Mortality</th>
<th>NNS</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSLT</td>
<td>53,454</td>
<td>≥ 30 pack yrs</td>
<td>LDCT vs CXR annually X3</td>
<td>20% decre.</td>
<td>6.7% decre.</td>
<td>320</td>
<td>good</td>
</tr>
<tr>
<td>DANTE</td>
<td>2,450</td>
<td>≥ 20 pack yrs</td>
<td>LDCT ann. X5 vs. single CXR/sputum</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>fair</td>
</tr>
<tr>
<td>DLCST</td>
<td>4,104</td>
<td>≥ 20 pack yrs</td>
<td>LDCT ann. X5 vs. usual care</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>fair</td>
</tr>
<tr>
<td>MILD</td>
<td>4,099</td>
<td>≥ 20 pack yrs</td>
<td>LDCT ann/bienn X 3 vs. usual care</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>poor</td>
</tr>
</tbody>
</table>
SCREENING FOR LUNG CANCER
U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

TARGET POPULATION
Asymptomatic adults aged 55 to 80 years of age who have a 30 pack-year smoking history and currently smoke or have quit smoking within the past 15 years

RECOMMENDATION
Screen annually for lung cancer with low-dose computed tomography. Discontinue screening when the patient has not smoked for 15 years. Grade: B

Annals of Internal Medicine 2014
What’s the Harm?

false positive results
false negative results
excess biopsies and complications
over-diagnosis
radiation exposure
cost
SCRENNED (1000 PEOPLE)

BENEFITS ADDED by Screening
18 PEOPLE DIED from lung cancer in a group of 1000 people who are screened. This was 3 FEWER DEATHS from lung cancer compared to the NOT SCREENED group.

HARMS ADDED by Screening
365 IN 1000 PEOPLE SCREENED experienced a FALSE POSITIVE result.
25 of those false positive results led to an INVASIVE PROCEDURE.
3 PEOPLE developed a MAJOR COMPLICATION from the invasive procedure.

NOT SCREENED (1000 PEOPLE)

21 PEOPLE DIED from lung cancer in a group of 1000 people who were not screened. This was 3 ADDITIONAL DEATHS from lung cancer compared to the group that was screened.
DNA Methylation

SAM = S-Adenosyl methionine
DNMT = DNA methyltransferase
A = adenine, C = cytosine, G = guanine, T = thymine
Mechanisms of Carcinogenesis through DNA Methylation

1. Cytosine methylation facilitates gene mutation as 5-methylcytosine is deaminated to thymine (C → T)

2. Aberrant DNA methylation may be associated with allelic loss through breaks in DNA.

3. Tumor suppressor genes may be inactivated by DNA hypermethylation.
Methodology

• 6 specific genes are highly methylated in NSCLC but not normal lung tissue
• Ongoing death of tumor cells releases DNA into sputum and blood
• Authors’ new technique permits detecting much smaller concentrations of methylated tumor DNA
Johns Hopkins Lung Cancer Program

a prospective observational cohort of 651 NSCLC patients

• 150 of these patients had early stage (T1-2, N0) cancer and underwent curative intent surgery

• 60 patients who underwent surgery for non-malignant lung lesions served as controls

• preoperative sputum and blood was assayed for methylated DNA of target genes in cases and controls
Using detection of methylated tumor genes as a test to differentiate NSCLC subjects from control subjects yields impressive Receiver Operator Curves.
Lung Cancer Prediction Models

sputum

- Sensitivity: 93%
- Specificity: 86%
- Positive Predictive Value: 91%

plasma

- Sensitivity: 93%
- Specificity: 67%
- Positive Predictive Value: 85%
In NSLT upon which LDCT screening is based:

False Positive Rate = 96.4%  PPV = 3.8%

When the sensitivity and specificity of the tumor gene DNA methylation test are applied to the NSLT population:

False Positive Rate = 91.8%  PPV = 8.2%
#4

PCSK9 again

(proprotein convertase subtilin-kexin type 9 inhibitor)
Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

ABSTRACT

Sabatine MS et al.
NEJM 2017
Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

In adults with clinically evident atherosclerotic cardiovascular disease, who had not achieved adequate LDL reduction with statin therapy, the administration of evolocumab, a monoclonal anti-PCSK9 antibody, every 2-4 weeks resulted in a 50% decrease in serum LDL concentrations and reduced cardiovascular events.
Proprotein Convertase Subtilisin/Kexin Type 9

LDLR bound to PCSK9 is digested in the lysosome

LDL-C is incorporated into the cell
A more clever way to reduce PCSK9

A normal component of our control system for gene expression is the production of RNA fragments (RNAi) which bind to specific mRNA and either block their translation into proteins or directs their destruction. An RNAi specific for PCSK9 mRNA has been created...
A Highly Durable RNAi Therapeutic Inhibitor of PCSK9

Kevin Fitzgerald, Ph.D., Suellen White, B.S.N., Anna Borodovsky, Ph.D., Brian R. Bettencourt, Ph.D., Andrew Strahs, Ph.D., Valerie Clausen, Ph.D., Peter Wijngaard, Ph.D., Jay D. Horton, M.D., Jorg Taubel, M.D., Ashley Brooks, M.B., Ch.B., Chamikara Fernando, M.B., B.S., Robert S. Kauffman, M.D., Ph.D., David Kallend, M.D., Akshay Vaishnaw, M.D., and Amy Simon, M.D.
INCLISIRAN

PCSK9 mRNA-specific RNAi bound to carbohydrate taken up by hepatocytes which then inhibits production of PCSK9 protein

Multiple-Dose (SC) Cohorts

**Inclisiran alone:**
- 125 mg weekly X4 (N=6)
- 250 mg weekly X2 (N=6)
- 300 mg monthly X2 (N=6)
- 500 mg monthly X2 (N=6)
- Placebo (N=8)

**Subjects**
- age 18 – 75 yrs
- LDL > 100 mg/dL
- 1/3 taking statins

**Inclisiran with statin:**
- 300 mg monthly X2 (N=3)
- 500 mg monthly X2 (N=5)
- Placebo (N=3)
ADVERSE EVENTS

No serious adverse events
Non-serious adverse events similarly distributed between active treatment and placebo subjects

CONCLUSION

Two injections of the PCSK9 RNAi decreased LDL levels by 50-60% for up to 7 months.
#5 Polypills
Prospective Urban Rural Epidemiology (PURE) study

A prospective, standardized cross-sectional analysis of baseline data to assess the prevalence, awareness, treatment, and control of hypertension by the economic status of countries and by sex, age group, location (urban vs rural), and education of the 58,000 participants worldwide.
Why can we not control hypertension?

- therapeutic inertia (*unjustified delay in treatment initiation or intensification*)
- low adherence rates
- complex guidelines
- multiple up-titration steps
Quarter-dose quadruple combination therapy for initial treatment of hypertension: placebo-controlled, crossover, randomised trial and systematic review

Clara K Chow, Jay Thakkar, Alex Bennett, Graham Hillis, Michael Burke, Tim Usherwood, Kha Vo, Kris Rogers, Emily Atkins, Ruth Webster, Michael Chou, Hakim-Moulay Dehbi, Abdul Salam, Anushka Patel, Bruce Neal, David Peiris, Henry Krum*, John Chalmers, Mark Nelson, Christopher M Reid, Mark Woodward, Sarah Hilmer, Simon Thom, Anthony Rodgers

Summary

Background Globally, most patients with hypertension are treated with monotherapy, and control rates are poor because monotherapy only reduces blood pressure by around 9/5 mm Hg on average. There is a pressing need for blood pressure-control strategies with improved efficacy and tolerability. We aimed to assess whether ultra-low-dose combination therapy could meet these needs.

Methods We did a randomised, placebo-controlled, double-blind, crossover trial of a quadpill—a single capsule containing four blood pressure-lowering drugs each at quarter-dose (irbesartan 37.5 mg, amlodipine 1.25 mg, hydrochlorothiazide 6.25 mg, and atenolol 12.5 mg). Participants with untreated hypertension were enrolled from four centres in the community of western Sydney, NSW, Australia, mainly by general practitioners. Participants were
The 4 most commonly used drug classes

- ACE-I/ARB
- β-blocker
- calcium-channel blocker
- thiazide/thiazide-like

“Full Dose”: the most frequently reported usual maintenance dose recorded by the British National Formulary

Quadpill: irbesartan 37.5 mg; amlodipine 1.25 mg; HCTZ 6.25 mg; atenolol 12.5 mg
Patients with untreated high blood pressure (two office blood pressure measures on two different days >140/90 mm Hg)

Baseline visit (week 0)
Clinical questionnaire, 24-h ambulatory blood pressure, blood tests

Randomise

- Week 0–4
  - Quadpill
  - Placebo
    - Visit 2 (week 4): 24-h blood pressure, blood tests, adverse events
    - 2-week washout
    - Visit 3 (week 6): 24-h blood pressure

- Week 4–6
  - Placebo
  - Quadpill

- Week 6–10
  - Placebo
  - Quadpill

Final visit (week 10): 24-h blood pressure, blood tests, adverse events, acceptability questionnaire

201Chow CK et al. Lancet 7
### Table 1: Baseline characteristics of trial participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 (11)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (48%)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (52%)</td>
</tr>
<tr>
<td>University education</td>
<td>9 (43%)</td>
</tr>
<tr>
<td>24-h systolic blood pressure/diastolic blood pressure (mm Hg)</td>
<td>140 (9)/87 (8)</td>
</tr>
<tr>
<td>Office systolic blood pressure/diastolic blood pressure (mm Hg)</td>
<td>154 (14)/90 (11)</td>
</tr>
<tr>
<td>Time since diagnosis of hypertension (months)</td>
<td>4.2 (5.4)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>5 (24%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>0</td>
</tr>
<tr>
<td>Coronary artery revascularisation</td>
<td>0</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>0</td>
</tr>
<tr>
<td>Previous depression</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>5 (46%)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or number of patients (%).
<table>
<thead>
<tr>
<th>BP</th>
<th>Quadpill</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>4 weeks</td>
</tr>
<tr>
<td>24hr syst</td>
<td>138.4</td>
<td>119.6</td>
</tr>
<tr>
<td>24 hr diast</td>
<td>86.7</td>
<td>73.3</td>
</tr>
<tr>
<td>Office syst</td>
<td>149.9</td>
<td>122.1</td>
</tr>
<tr>
<td>Office diast</td>
<td>87.4</td>
<td>71.8</td>
</tr>
</tbody>
</table>

Chow CK et al. Lancet 2017
Treatment Adherence during Week 4
placebo: 0.3 pills missed
quadpill: 0.2 pills missed

One Pill
No titration
No stepwise addition
Minimal side-effects
Holy Grail of Treating Hypertension?
#6
Endobronchial Valves for Homogeneous Emphysema
Lung volume reduction has been shown to improve function and survival in patients with *heterogeneous* emphysema:
Similar changes in lung dynamics can be achieved with the use of endobronchial valves:

Alifano M et al. Eur Respir Rev 2010
Endobronchial Valve Therapy in Patients with Homogeneous Emphysema
Results from the IMPACT Study

Arshang Valipour1, Dirk-Jan Slebos2, Felix Herth3, Kaid Darwiche4, Manfred Wagner5, Joachim H. Ficker5, Christoph Petermann6, Ralf-Harto Hubner7, Franz Stanzel8, and Ralf Eberhardt3; for the IMPACT Study Team

1Ludwig Boltzmann Institute for COPD and Respiratory Epidemiology, Otto Wagner Spital, Vienna, Austria; 2Department of Pulmonary Diseases, University of Groningen, and University Medical Center Groningen, Groningen, the Netherlands; 3Department of Pneumology and Critical Care Medicine, Thoraxklinik, University of Heidelberg and Translational Lung Research Center Heidelberg, German Center for Lung Research, Heidelberg, Germany; 4Department of Interventional Pneumology, Ruhrlandklinik, West German Lung Center, University Clinic Essen, Essen, Germany; 5Department of Respiratory Medicine, Allergology and Sleep Medicine, General Hospital Nuernberg, and Paracelsus Medical University, Nuremberg, Germany; 6Lungenabteilung, Thoraxzentrum Hamburg, Asklepios Klinik, Hamburg, Germany; 7Charité Campus Virchow-Klinikum, Berlin, Germany; and 8Lungenklinik Hemer, Hemer, Germany
Can the benefits of lung volume reduction extend to patients with *homogeneous* emphysema?

- 183 adult former smokers with severe emphysema randomized to usual care or EBV placement
- FEV1 15% - 45% predicted; RV ≥ 200% predicted
- homogeneous emphysema (< 15% difference between lobes in tissue loss per CT)
- perfusion difference between lungs < 20%
- targeted lobe with highest CT destruction score
INTERVENTION

• placement of endobronchial valves in all segments/sub-segments of target lobe to achieve lobar occlusion
• if total lobar occlusion not achieved, repeat bronchoscopy and valve placement at 30 days
• 3 months after final bronchoscopy, assessment with
  PFTs
  CT to assess degree of target lobe volume reduction
  6-minute walk test
  St. George Respiratory Questionnaire
  modified Medical Research Council dyspnea index
  COPD Assessment Test
  BODE (BMI; airflow obstruction; dyspnea; exercise capacity) index
RESULTS

Randomized: EBV 43 Control 50. Completed protocol: EBV 33 Control 46

A

ITT Population: FEV1

p = 0.0002
Δ = 17.0%

B

PP Population: FEV1

p = 0.0003
Δ = 19.3%
What percentage of subjects achieved a clinically meaningful outcome?

Table 3. Responders with Minimal Clinically Important Difference in Key Outcome Measures in Intention-to-Treat Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>EBV Group</th>
<th>SoC Group</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (L), † MCID ≥ +15%</td>
<td>15/43 (34.9%)</td>
<td>2/50 (4.0%)</td>
<td>0.00001</td>
</tr>
<tr>
<td>FEV₁ (L), † MCID ≥ +12%</td>
<td>17/43 (39.5%)</td>
<td>4/50 (8.0%)</td>
<td>0.00003</td>
</tr>
<tr>
<td>FEV₁ (L), MCID ≥ 100 ml</td>
<td>16/43 (37.2%)</td>
<td>5/50 (10.0%)</td>
<td>0.002</td>
</tr>
<tr>
<td>RV (ml), MCID ≤ -430 ml</td>
<td>19/43 (44.2%)</td>
<td>9/50 (18.0%)</td>
<td>0.006</td>
</tr>
<tr>
<td>SGRQ, MCID ≤ -4 points</td>
<td>21/37 (56.8%)</td>
<td>12/48 (25.0%)</td>
<td>0.003</td>
</tr>
<tr>
<td>SGRQ, MCID ≤ -8 points</td>
<td>17/37 (45.9%)</td>
<td>4/48 (8.3%)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>6MWD, MCID ≥ +26 m</td>
<td>20/40 (50.0%)</td>
<td>7/50 (14.0%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>mMRC, MCID ≤ -1 point</td>
<td>17/41 (41.5%)</td>
<td>7/50 (14.0%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Definition of abbreviations: 6MWD = 6-minute-walk distance; EBV = endobronchial valve; MCID = minimal clinically important difference; mMRC = modified Medical Research Council; RV = residual volume; SGRQ = St. George’s Respiratory Questionnaire; SoC = standard of care.
ADVERSE EVENTS

One quarter of EBV subjects had a pneumothorax

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>EBV Group (n = 43)</th>
<th>SoC Group (n = 50)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total respiratory SAEs, n</td>
<td>26 (44.2%)</td>
<td>8 (12.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>COPD exacerbation with hospitalization</td>
<td>10 (16.3%)</td>
<td>6 (12.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1 (2.3%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>1 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>1 (2.3%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>12 (25.6%)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resolved ≤ 14 d after onset, with drainage§</td>
<td>8 (16.3%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Required temporary valve removal</td>
<td>2 (4.6%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Required permanent valve removal because of recurrent pneumothorax</td>
<td>1 (2.3%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Required permanent valve removal, after temporary removal and reimplantation, because of recurrent pneumothorax</td>
<td>2 (4.6%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Other EBV-related events requiring valve replacement</td>
<td>3 (7.0%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Valve migration</td>
<td>2 (4.6%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Paralysis of the nervus recurrens</td>
<td>1 (2.3%)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>
SUMMARY

• first prospective, multi-center RCT of endobronchial valve therapy in subjects with homogeneous emphysema
• 90% of EBV subjects achieved adequate lung volume reduction
• EBV therapy resulted in statistically and **clinically significant improvement in lung function, exercise capacity, and quality of life**

• small sample size with short follow-up
• significant treatment-related pneumothorax rate
• 7% of treatment group required revision of valve placement due to valve migration
• trial not designed to measure long term outcomes such as mortality
Gene Therapy and Neovascular Age-Related Macular Degeneration
Age-related macular degeneration (AMD)

- leading cause of low vision in elderly in developed world
- 90% of severe cases involve neovascular (“wet”) AMD
- intraocular injection of VEGF inhibitors can control neovascularization and improve vision
- control of neovascularization requires monthly injection of VEGF inhibitors
- recent study demonstrated efficacy of *intraretinal* injection of adenovirus carrying anti-VEGF gene, but procedure is not routinely performed by most opthalmologists
Adeno-Associated Virus Vector

- non-pathogenic in humans
- minimally immunogenic
- able to carry specific human genes
- able to infect dividing and non-dividing cells
- attached human gene is transcribed and processed to form active protein
AAV2-sFLT01
• adeno-associated virus carrying sFLT01
• sFLT01: VEGF-neutralizing protein gene
• injected into mouse vitreous, the VEGF-neutralizing gene is incorporated into retinal ganglion cells

Intravitreal injection of AAV2-sFLT01 in patients with advanced neovascular age-related macular degeneration: a phase 1, open-label trial

Jeffrey S Heier, Saleema Kherani, Shilpa Desai, Pravin Dugel, Shalesh Kaushal, Seng H Cheng, Cheryl Deacono, Annie Purvis, Susan Richards, Annaig Le-Halpere, John Connelly, Samuel CWadsworth, Rafael Varona, Ronald Buggage, Abraham Scaria, Peter A Campochiaro

Summary

Background Long-term intraocular injections of vascular endothelial growth factor (VEGF)-neutralising proteins can preserve central vision in many patients with neovascular age-related macular degeneration. We tested the safety and tolerability of a single intravitreal injection of an AAV2 vector expressing the VEGF-neutralising protein sFLT01 in patients with advanced neovascular age-related macular degeneration.

Heier JS et al. Lancet 2017
Phase 1, Open-Label, Safety and Tolerability Study

- 19 patients with advanced neovascular age-related macular degeneration
- single *intravitreous* injection of AAV2-sFLT01
- dosing tested on cohorts 1-4
- maximal dose administered to cohort 5, patients who had previously responded to monthly VEGF inhibitor injections

(Heier JS et al. Lancet 2017)
RESULTS

• 52-week follow-up
• Maximal Tolerated Dose was not reached
• 2 treatment-related adverse events
  ▪ transient fever
  ▪ intraocular inflammation, resolved with steroids
• half of the highest dose cohorts had measurable concentrations of sFLT01 gene product in their vitreous

Heier JS et al. Lancet 2017
CST = Central Subfield Thickness

Heier JS et al. Lancet 2017
Resolution of Macular Edema

Sequential horizontal optical coherence scan through the fovea of two patients with dramatic, sustained reduction of macular fluid after an intravitreous injection of AAV2-sFLT01

Heier JS et al. Lancet 2017
CONCLUSIONS

• Single intravitreous inject of AAV2-sFLT01 can produce adequate concentrations of VEGF-neutralizing factor for stabilization of vision in neovascular AMD.
• ~60% of higher-dose subjects exhibit increase in anti-AAV2 antibodies
• adverse events are infrequent and transient
• no maximal tolerated dose was reached, hence higher doses must be tested for safety and efficacy
#8 HOT FLASHES
“Hot flushes are characterized by a transient and intense sensation of heat accompanied by the activation of heat-loss effectors including skin vasodilatation, sweating, and cold-seeking behavior.”
Rance NE et al. Front Neuroendocrin 2013

Median duration of hot flashes is 7.4 years

10% of women experience hot flashes as “intolerable”

Peripheral infusion of neurokinin B intravenously to healthy premenopausal women induces hot flashes
Female Reproductive – Thermoregulatory System Integration

- core temperature varies by 0.3–0.5 C across the menstrual cycle
- body temperature is modulated during pregnancy
- hot flashes occur during menopause
Estrogen withdrawal leads to hypertrophy of hypothalamic neurons expressing these hormones. These neurons project into thermoregulatory centers.

KISS: kisspeptin
NKB: neurokinin B
SP: substance P
DYN: dynorphin

Rance NE et al. Front Neuroendocrin 2013
“Eligible participants were healthy women aged 40–62 years, having seven or more hot flushes in every 24 h of which some were reported as being severe or bothersome, who had not had a menstrual period for at least 12 months, and who had not been taking any medication shown to improve menopausal flushes in the preceding 8 weeks.”

Prague JK et al. Lancet 2017
- oral NK3R antagonist
- randomised
- placebo-controlled
- double-blind
- crossover trial

37 subjects randomized (intention to treat)
28 completed protocol (per protocol)

Prague JK et al. Lancet 2017
Intention to treat analysis (n = 37) Prague JK et al. Lancet 2017
# Secondary Outcomes

**Per Protocol Analysis (n = 28)**  
**MENQOL: Menopause-Specific Quality of Life**  
Prague JK et al. Lancet 2017

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (adjusted mean)</th>
<th>MLE4901 (adjusted mean)</th>
<th>p value comparing adjusted treatment means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flush severity</td>
<td>5.70 (5.09 to 6.38)</td>
<td>3.27 (2.92 to 3.66)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hot flush bother</td>
<td>5.56 (4.96 to 6.22)</td>
<td>2.92 (2.61 to 3.27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hot flush interference</td>
<td>26.48 (20.02 to 35.03)</td>
<td>7.94 (5.76 to 10.95)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>MENQOL domain score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasomotor</td>
<td>3.98 (3.38 to 4.69)</td>
<td>2.05 (1.74 to 2.42)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>2.58 (2.30 to 2.90)</td>
<td>2.18 (1.94 to 2.45)</td>
<td>0.0083</td>
</tr>
<tr>
<td>Physical</td>
<td>2.93 (2.63 to 3.27)</td>
<td>2.42 (2.17 to 2.69)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Sexual</td>
<td>2.15 (1.84 to 2.51)</td>
<td>1.98 (1.68 to 2.30)</td>
<td>0.24</td>
</tr>
<tr>
<td>Number of flushes detected by sweat monitor</td>
<td>26.91 (23.16 to 31.27)</td>
<td>16.22 (13.99 to 18.80)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
### Adverse Events

Maximal Increase 5.9 x upper limit of normal
All ALT & AST elevations returned to baseline

<table>
<thead>
<tr>
<th>Condition</th>
<th>Baseline</th>
<th>Placebo</th>
<th>MLE4901</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT increased (grade 1) with normal AST</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>AST increased (grade 1) with normal ALT</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>ALT increased (grade 1) with AST increased (grade 1)</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>ALT increased (grade 2) with AST increased (grade 1)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>ALT increased (grade 3) with AST increased (grade 1)</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Blood bilirubin increased (grade 1)</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alkaline phosphatase increased (grade 1)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Creatinine increased (grade 1)</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Prague JK et al. Lancet 2017
Achievement of Diabetes Treatment Goals

A Glycated Hemoglobin (%)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10</td>
<td>16.9</td>
<td>22.5</td>
<td>17.6</td>
</tr>
<tr>
<td>9.0–9.9</td>
<td>27.3</td>
<td>34.3</td>
<td>34.9</td>
</tr>
<tr>
<td>8.0–8.9</td>
<td>22.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.0–7.9</td>
<td>14.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.0–6.9</td>
<td>6.3</td>
<td>9.6</td>
<td>9.4</td>
</tr>
<tr>
<td>&lt;6.0</td>
<td>12.6</td>
<td>7.3</td>
<td>6.8</td>
</tr>
</tbody>
</table>

P=0.009

Ali MK et al. NEJM 2013
90% of patients with T2DM have an excess body weight.

Effective weight loss in obese subjects with T2DM is associated with improvements of metabolic condition.
### Previous Bariatric Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Site</th>
<th>Intervention</th>
<th>No</th>
<th>BMI (kg/m²)</th>
<th>Follow-Up (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ikramuddin et al&lt;sup&gt;21&lt;/sup&gt; 2015</td>
<td>USA and Taiwan</td>
<td>RYGB</td>
<td>60</td>
<td>34.9 ± 3.0</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical</td>
<td>60</td>
<td>34.3 ± 3.1</td>
<td></td>
</tr>
<tr>
<td>Courcoulas et al&lt;sup&gt;20&lt;/sup&gt; 2015</td>
<td>USA</td>
<td>RYGB</td>
<td>24</td>
<td>35.5 ± 2.6</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical</td>
<td>23</td>
<td>35.7 ± 3.3</td>
<td></td>
</tr>
<tr>
<td>Halperin et al&lt;sup&gt;28&lt;/sup&gt; 2014</td>
<td>USA</td>
<td>RYGB</td>
<td>19</td>
<td>36.0 ± 3.5</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical</td>
<td>19</td>
<td>36.5 ± 3.4</td>
<td></td>
</tr>
<tr>
<td>Schauer et al&lt;sup&gt;30&lt;/sup&gt; 2014</td>
<td>USA</td>
<td>RYGB</td>
<td>50</td>
<td>37.0 ± 3.3</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical</td>
<td>50</td>
<td>36.8 ± 3.0</td>
<td></td>
</tr>
<tr>
<td>Liang et al&lt;sup&gt;29&lt;/sup&gt; 2013</td>
<td>China</td>
<td>RYGB</td>
<td>31</td>
<td>30.48 ± 0.94</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical*</td>
<td>34</td>
<td>30.28 ± 1.44</td>
<td></td>
</tr>
<tr>
<td>Mingrone et al&lt;sup&gt;22&lt;/sup&gt; 2015</td>
<td>Italy</td>
<td>RYGB</td>
<td>20</td>
<td>44.85 ± 5.16</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical</td>
<td>20</td>
<td>45.62 ± 6.24</td>
<td></td>
</tr>
</tbody>
</table>

The lone 5-year study had only 40 subjects.

Young Yan MM et al. Medicine 2016
Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 5-Year Outcomes


Schauer PR et al. NEJM 2017
Randomized, Controlled, Prospective Trial

Intensive Medical Therapy

vs.

Roux-en-Y Gastric Bypass

vs.

Sleeve Gastrectomy

150 subjects
Avg. Age 48 yrs
Avg. BMI 37
1/3 BMI < 35
Using Insulin 44%

Schauer PR et al.
NEJM 2017
Primary Endpoint

\[ \text{HgbA1c} \leq 6.0 \text{ at 5 years} \]

Med Ther: 5%
RYGB: 29%
Sleeve: 23%

Schauer PR et al. NEJM 2017
A Glycated Hemoglobin

Glycated Hemoglobin Level (%)

Month

Mean (median) Value at Visit

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>42</th>
<th>54</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical therapy</td>
<td>8.8</td>
<td>7.3</td>
<td>7.5</td>
<td>8.4</td>
<td>8.6</td>
<td>8.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(8.6)</td>
<td>(7.2)</td>
<td>(8.2)</td>
<td></td>
<td>(8.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric bypass</td>
<td>9.3</td>
<td>6.4</td>
<td>6.5</td>
<td>6.8</td>
<td>6.8</td>
<td>7.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(9.4)</td>
<td>(6.2)</td>
<td>(6.4)</td>
<td></td>
<td>(6.6)</td>
<td>(6.8)</td>
<td>(6.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleeve gastrectomy</td>
<td>9.5</td>
<td>6.7</td>
<td>6.8</td>
<td>7.0</td>
<td>7.1</td>
<td>7.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(8.9)</td>
<td>(6.4)</td>
<td>(6.8)</td>
<td></td>
<td>(6.7)</td>
<td>(6.6)</td>
<td>(7.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Schauer PR et al. NEJM 2017
After 5 years, 45% of the RYGB subjects required no glucose-lowering medications.
Schauer PR et al. NEJM 2017
Other Outcomes

- duration of DM < 8 years positively predicted HgbA1c < 6
- surgery was equally effective in lowering HgbA1c for BMI > 35 vs. BMI < 35
- HDL↑’d 7% w/ Med Ther vs. 31% w/ surgery
- triglycerides ↓’d 8% w/ Med Ther; ↓’d 40% w/ RYGB; ↓’d 29% w/ Sleeve

Schauer PR et al. NEJM 2017
Adverse Events

- 5 surgical subjects required surgical revisions

> 5% increase in body weight: 19% Med Ther subjects vs. 0% surgery subjects

- mild anemia occurred in 38% of surgery subjects vs. 16% of Med Ther subjects

Schauer PR et al. NEJM 2017
Prostate Cancer Intervention versus Observation Trial (PIVOT)

19.5 years follow-up
Trial Description

- Enrolled 731 men with localized prostate cancer from 1994 - 2002
- all tumor grades included
- PSA < 50
- subject must be medically fit for radical prostatectomy
- age ≤ 75 years
- life-expectancy of at least 10 years

Randomized to radical prostatectomy vs. observation (treatment for symptomatic or metastatic disease only)

Average age 67 years    Median PSA 7.8

Wilt TJ et al. NEJM 2017
Cumulative incidence of death:
surgery 61.3%     observation 66.8%     $p = 0.06$

Wilt TJ et al. NEJM 2017
Cumulative incidence of death:
surgery 7.4%  observation 11.4%  p = 0.06

Wilt TJ et al. NEJM 2017
surgery risk of death/observation risk of death = 0.84

95% confidence interval: 0.70 – 1.01

surgery risk of prostate cancer death/observation risk of prostate cancer death = 0.63

95% confidence interval: 0.39 – 1.02

Wilt TJ et al. NEJM 2017
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Observation</th>
<th>Radical Prostatectomy</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>245/367</td>
<td>223/364</td>
<td>0.84 (0.70–1.01)</td>
<td>0.56</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>78/131</td>
<td>58/122</td>
<td>0.73 (0.52–1.02)</td>
<td></td>
</tr>
<tr>
<td>≥65 yr</td>
<td>167/236</td>
<td>165/242</td>
<td>0.88 (0.71–1.09)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>White</td>
<td>155/220</td>
<td>150/232</td>
<td>0.82 (0.66–1.03)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>75/121</td>
<td>64/111</td>
<td>0.87 (0.62–1.22)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>15/26</td>
<td>9/21</td>
<td>0.64 (0.28–1.46)</td>
<td></td>
</tr>
<tr>
<td>PSA</td>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>≤10 ng/ml</td>
<td>151/241</td>
<td>140/238</td>
<td>0.91 (0.72–1.14)</td>
<td></td>
</tr>
<tr>
<td>&gt;10 ng/ml</td>
<td>93/125</td>
<td>83/126</td>
<td>0.73 (0.54–0.98)</td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>Low</td>
<td>83/148</td>
<td>82/148</td>
<td>0.98 (0.72–1.33)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>89/120</td>
<td>77/129</td>
<td>0.68 (0.50–0.92)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>59/80</td>
<td>55/77</td>
<td>0.78 (0.54–1.13)</td>
<td></td>
</tr>
<tr>
<td>Charlson score</td>
<td></td>
<td></td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>0</td>
<td>128/220</td>
<td>117/224</td>
<td>0.84 (0.65–1.07)</td>
<td></td>
</tr>
<tr>
<td>≥1</td>
<td>117/147</td>
<td>106/140</td>
<td>0.85 (0.65–1.10)</td>
<td></td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
<td></td>
<td>0.55</td>
</tr>
<tr>
<td>0</td>
<td>200/310</td>
<td>184/312</td>
<td>0.84 (0.69–1.03)</td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>45/57</td>
<td>39/52</td>
<td>0.83 (0.54–1.28)</td>
<td></td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
<td></td>
<td>0.84</td>
</tr>
<tr>
<td>&lt;7</td>
<td>167/261</td>
<td>145/254</td>
<td>0.82 (0.65–1.02)</td>
<td></td>
</tr>
<tr>
<td>≥7</td>
<td>63/86</td>
<td>68/98</td>
<td>0.83 (0.59–1.17)</td>
<td></td>
</tr>
</tbody>
</table>

Wilt TJ et al. NEJM 2017
Box. Risk Stratification Schema for Prostate Cancer

National Comprehensive Cancer Network Risk Stratification

Very low risk
Clinical stage of T1c, Gleason score of 6 or less, prostate-specific antigen (PSA) level of less than 10 ng/mL, less than 3 biopsy cores with cancer presence of 50% or less in each core, and PSA density of less than 0.15 ng/mL/g

Low risk
Clinical stage of T1 to T2a, Gleason score of 6 or less, and PSA level of less than 10 ng/mL

Intermediate risk
Clinical stage of T2b to T2c, Gleason score of 7, or PSA level of 10 to 20 ng/mL

High risk
Clinical stage of T3a, Gleason score of 8 to 10, or PSA level greater than 20 ng/mL

Very high risk
Clinical stage of T3b to T4, primary Gleason pattern 5, or greater than 4 biopsy cores with Gleason score of 8 to 10

Litwin MS and Tan H-J. JAMA 2017

T2b: tumor involves more than ½ of one lobe only

T2c: tumor involves both lobes
## Adverse Events Requiring Treatment

<table>
<thead>
<tr>
<th>Condition</th>
<th>Surgery</th>
<th>Observance</th>
<th>Absolute Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erectile dysfunction</td>
<td>14.6%</td>
<td>5.4%</td>
<td>9.1% (4.8 – 13.5%)</td>
</tr>
<tr>
<td>Incontinence</td>
<td>17.3%</td>
<td>4.4%</td>
<td>12.9% (8.6 – 17.5%)</td>
</tr>
</tbody>
</table>

Wilt TJ et al. NEJM 2017
My conclusions:

1. Radical prostatectomy in moderate risk patients improves long term survival at the expense of increased erectile dysfunction and urinary incontinence.

2. Improving risk stratification should lead to more accurate identification of who can really benefit from surgery.

3. Improving active surveillance could allow us to identify those who initially at low risk are progressing to a higher risk where timely surgery could then improve survival.