Health Screening Update: Prostate Cancer

Zamip Patel, MD
FSACOFP Convention
August 1st, 2015
Outline

• Epidemiology of prostate cancer
• Purpose of screening
• Method of screening
• Contemporary screening trials
• Current Guidelines
• Future directions
Key Questions

• Should all men be screened?
• Who should be offered screening?
• How should men be screened?
Key Questions

- Does screening extend men’s lives (are there benefits)?
- Does screening lead to health problems (are there harms)?
- Do the benefits outweigh the harms? (are there harms)?
Prostate Cancer: Epidemiology

- Most common non-skin cancer in men
- Second leading cause of cancer death (30,000) in U.S. men
- Approximately 240,000 new cases of prostate cancer are being diagnosed annually in USA
- Every year younger and healthier men are being diagnosed with localized prostate cancer, with an annual percentage increase of approximately 9.5%, (SEER) registry
Risk Factors

• Age: Incidence 1 in 55 in age group 40-60 yrs;
  ○ 1 in 7 in 60-80 yrs age group

• Family history of Prostate ca:
  ➢ First degree relative: Double risk
  ➢ Relative dx under age 60: Four times risk

• Race: incidence in African Americans > Caucasians
### New Cases and Death Estimates in USA

**Estimated New Cases**

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>233,000</td>
<td>27%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>116,000</td>
<td>14%</td>
</tr>
<tr>
<td>Colorectum</td>
<td>71,830</td>
<td>8%</td>
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<tr>
<td>Urinary bladder</td>
<td>56,390</td>
<td>7%</td>
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<tr>
<td>Melanoma of the skin</td>
<td>43,890</td>
<td>5%</td>
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<tr>
<td>Kidney &amp; renal pelvis</td>
<td>39,140</td>
<td>5%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>38,270</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>30,220</td>
<td>4%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>30,100</td>
<td>4%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>24,600</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>855,220</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

**Estimated Deaths**

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>86,930</td>
<td>28%</td>
</tr>
<tr>
<td><strong>Prostate</strong></td>
<td><strong>29,480</strong></td>
<td><strong>10%</strong></td>
</tr>
<tr>
<td>Colorectum</td>
<td>26,270</td>
<td>8%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>20,170</td>
<td>7%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>15,870</td>
<td>5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>14,040</td>
<td>5%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,450</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>11,170</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>10,470</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,900</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>310,010</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
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Cancer Screening:
Both Prostate & Breast Have Been Scrutinized
Purpose of Screening

- Early detection of potentially lethal malignancy
- Early treatment
- Improved survival
PSA screening: Impact

• The mortality rate from prostate cancer is 45% lower than it was in 1992

• 50-70% of this decrease is attributed to PSA screening

Cancer Incidence and Mortality Rates

age-adjusted, standardized over time
Estimated Prevalence of PSA screening by Year and Age in the U.S.

- High level of PSA testing being done in elderly men who are unlikely to benefit from screening
- Relatively low level of testing in young men who are most in need of early diagnosis

Current Method of Screening

- **Digital Rectal Exam**
  - Subjective

- **Serum Prostate Specific Antigen (PSA)**
  - Not specific
Prostate Cancer Screening Trials
• PLCO trial
• 1993 -2001
• Screening arm:38,350
• Control arm:38,350
• PSA annually x 6 yrs
• DRE annually x 4 yrs
• Follow up: 7 -10 yrs
PLCO trial

- Incidence of Ca prostate
- Screening: 116/10,000-2820
- Control: 95/10,000-2322
- Relative increase of 22% in rate of Ca prostate diagnosis in screening arm
PLCO : Death Rates

- Incidence of Ca prostate deaths:
  - Screening:2/10,000 (50)
  - Control:1.7/10,000(44)
- Conclusion: No significant difference in rate of death from Ca prostate in 2 groups at 7 years follow up
Challenges to The PLCO Trial Data

- 40%-52% contamination in control group each year
- 74% men in control group: screened at least once
- Biopsy rate for those with elevated PSA: relatively low: might have missed aggressive Ca prostate in 3.0-3.9 ng/ml group
- Did not test hypothesis; value of PSA screening
- Extremely short follow up
Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Antonio Berenguer, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*

182,160 Subjects 50–74 yr old underwent randomization
162,387 Were in the core age group (55–69 yr old)

160 Subjects 50–74 yr old died
144 Were 55–69 yr old

82,816 Were assigned to the screening group
72,890 Were 55–69 yr old

6830 Had prostate cancer
5990 Were 55–69 yr old

99,184 Were assigned to the control group
89,353 Were 55–69 yr old

4781 Had prostate cancer
4307 Were 55–69 yr old

Figure 1. Enrollment and Outcomes, According to Age Group at Randomization.
The predefined core age group for this study included 162,243 men between the ages of 55 and 69 years.

- Multicentric ERSPC trial
- PSA screening at 4 yrs interval
- Prostate Biopsy: PSA ≥ 3 ng/ml
- Median follow up: 9 years
ESPREE trial 9 years follow up

- Cumulative incidence of prostate cancer:
  - Screening: 8.2%
  - Control: 4.8%
- Rate ratio for death from Ca prostate in screening group: 0.80 vs control ($p = 0.04$)
ESPRC trial 9 years follow up

• PSA-based screening reduced the rate of death from prostate cancer by 20%

• High risk of overdiagnosis

• To prevent 1 Prostate CA death:
  o 1410 men need to be screened
  o 48 cases of prostate cancer need to be treated
Prostate-Cancer Mortality at 11 Years of Follow-up

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Alvaro Páez, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Sigrid Carlsson, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Paula M. Kujala, M.D., Bert G. Blijenberg, Ph.D., Ulf-Hakan Stenman, M.D., Andreas Huber, M.D., Kimmo Taari, M.D., Matti Hakama, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*

ERSPC (11 yrs follow up)

- 162,243 men randomized
- Screening q 2-4 years vs. usual care
- 11 years of follow up (median)
- Detection was higher in screening group
  - 6963 cases vs. 5396, or cumulative incidence of 9.6% vs. 6.0%
At 11 years, 299 prostate-cancer deaths in screening group and 462 in the control group. Rate ratio 0.79, 95% confidence interval 0.68-0.91, \( p=0.003 \).

**Figure 2.** Cumulative Hazard of Death from Prostate Cancer among Men 55 to 69 Years of Age.

Values are not included for centers in France because of the short follow-up period (median, 4.6 years). The Nelson–Aalen method was used to calculate the cumulative hazard of death from prostate cancer.
ERSPC (11 yrs follow up): Conclusions

• Screening → 21% reduction in prostate-cancer death*

• To prevent 1 prostate cancer death:
  ➢ Number needed to screen: 1055
  ➢ Number needed to treat: 37

* Up to 29% reduction if corrected for noncompliance in the screening arm and contamination of the control arm
Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up


- Study: ERSPC multicentric, 1993-2005
- Screening interval: 4 years (2 yrs in Sweden)
- Prostate biopsy: PSA ≥ 3.0 ng/ml

Lancet Oncology 2014; 384: 2027–35
ERSPC trial (13 yrs follow up)

- Ca prostate incidence:
  - Screening: 9.55/1000
  - Control: 6.23/1000 person yrs

- $P = 0.001$

*Figure 2: Nelson-Aalen estimates of cumulative prostate cancer mortality (all centres, excluding France)*
ERSPC trial (13 yrs follow up)

Conclusion:
- Significant 21% relative reduction in prostate cancer mortality in favor of PSA screening
- To prevent 1 prostate cancer death
  - 781 need to be screened
  - 27 treated
- RR reduction: 27% after adjustment selection effects
Mortality results from the Göteborg randomised population-based prostate-cancer screening trial

Jonas Hugosson, Sigrid Carlsson, Gunnar Aus, Svante Bergdahl, Ali Khatami, Pär Lodding, Carl-Gustaf Pihl, Johan Stranne, Erik Holmberg, Hans Lilja

PSA testing: every 2 yrs
Median follow up: 14 yrs

Lancet Oncol 2010; 11: 725–32
Goteborg Trial (14 yrs follow up)

Cumulative Ca prostate incidence:
- Screening: 12.7%
- Control: 8.2%
- P < 0.0001

Figure 2: Cumulative incidence of prostate cancer in the screening group and in the control group
Goteborg Trial (14 yrs follow up)

Absolute cumulative risk reduction in Ca prostate mortality:
- Screening: 0.5%
- Control: 0.9% (p < 0.001)

Rate ratio of Ca prostate mortality:
- Screening vs control: 0.56
- P = 0.002
Conclusion: Goteborg Trial (14 yrs follow up)

- Prostate ca mortality reduced by 50% over 14 yrs in screening group
- To prevent 1 prostate cancer death
  - 293 men needed to be screened
  - 12 to be diagnosed
- Number needed to treat (NNT) and benefits of PSA screening: comparable to breast cancer screening program
How does prostate cancer screening efficacy compare with screening for other common cancers?
Breast Cancer Screening

- CISNET and STS
- Number needed to screen:
  - STS: 465
  - CISNET:
    - 40-49 years: 746
    - 50-59 years: 351
    - 60-69 years: 233
    - 70-79 years: 377

Colon Cancer Screening

- PCLO
  - Flexible sigmoidoscopy
- Relative risk reduction 12 years:
  - Incidence 21%
  - Cancer specific death 26%
- Number needed to screen: 871

Schoen et al. NEJM 2012
Sub-set analysis of men with no comorbidities (that predict cardiovascular or cancer mortality)

Adjusted hazard ratio for screening group vs. unscreened group was 0.56 (0.33-0.95), p=0.03.

Number needed to treat to prevent one PCa death at 10 years was 5.

Crawford et al, JCO 2011
Summary of Randomized Trial Data on Screening

- **PLCO**
  - No benefit of screening
  - Flawed due to contamination of the control arm

- **ERSPC**
  - 21% relative risk reduction
  - 781 needed to screen; 27 needed to treat

- Screening may be beneficial
  - In younger, healthier men
  - High risk patients
  - Targeted screening reduces NNS to ~300 and NNT to 10 or 12.
PSA screening guidelines

"C'mon, c'mon — it's either one or the other."
USPTF guidelines (2012)

• The Task Force recommends against PSA-based screening for prostate cancer: Grade D (2012)
• More men will be harmed by PSA screening than will benefit
• The expected harms are greater than the small potential benefit

USPTF guidelines (2012)

- Some men are being diagnosed who do not have a significant cancer
- Some men are being treated who would possibly not die of the disease
- But how do you differentiate these men?
- There is no tool to make this differentiation
• PSA screening in men < age 40 years: not recommended

• Routine screening in men between ages 40 to 54 years at average risk: not recommended

• For men ages 55 to 69 years: shared decision-making is recommended and proceeding based on patients’ values and preferences

Carter HB et al., J Urol 2013;190:419-26
AUA guidelines (2013)

- To reduce the harms of screening: a routine screening interval of two years or more may be preferred over annual screening.

- Men over age 70 or any man with less than a 10-15 year life expectancy: routine PSA screening not recommended.

Carter HB et al, J Urol 2013;190:419-26
Doctors should start conversing with men about the potential benefits, uncertainties, and risks of Prostate Cancer Screening in the following risk categories:

• Very high risk - (men with more than one first degree relative) begin the conversation at age 40

• High risk - (men of African American descent and/or those who have a single first degree relative - father, brother or son diagnosed with prostate cancer before age 65) begin the conversation at age 45
Florida Hospital Cancer Institute guidelines

- Average risk - begin conversation at age 50

- Screening: PSA and Digital Rectal Exam

- Men with less than 10-15 year life expectancy: should not be offered Prostate Cancer Screening

- The exact interval (yearly, biennial, or every 4 years) of subsequent Prostate Cancer Screenings: still uncertain - pros and cons of future screening intervals should be discussed with each patient

*Based on recommendations of FHCI expert panel, AUA and ACS guidelines*
Comparison of various PSA screening guidelines
<table>
<thead>
<tr>
<th>Organization</th>
<th>Year established</th>
<th>Baseline testing age</th>
<th>Invitation to screening (age in yrs)</th>
<th>High risk groups (age in yrs)</th>
<th>Screening interval</th>
<th>PSA threshold For biopsy (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Cancer Society</td>
<td>2015</td>
<td>None</td>
<td>At 50 years with life expectancy ≥ 10 years</td>
<td>45 yrs:African Americans,f irst degree relative with prostate ca &lt; 65 yrs 40 years:if &gt; 1 first degree relative )</td>
<td>PSA ≥ 2.5: yearly PSA &lt; 2.5 : 2 years</td>
<td>4.0: in most patients 2.5: high risk patients</td>
</tr>
<tr>
<td>USPSTF</td>
<td>2012</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>AUA</td>
<td>2013</td>
<td>None</td>
<td>55-69</td>
<td>40-69</td>
<td>2 yearly</td>
<td>None specified</td>
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</tbody>
</table>

*Kim EH et al , BMC Medicine 2015;61:1-4*
<table>
<thead>
<tr>
<th>Organization</th>
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</tr>
</thead>
<tbody>
<tr>
<td>EUA</td>
<td>2013</td>
<td>40-45</td>
<td>Any age with life expectancy ≥ 10 years</td>
<td>Any age with life expectancy ≥ 10 years</td>
<td>Every 2-4 years if baseline PSA &gt; 1 ng/ml Every 8 years if PSA ≤ 1</td>
<td>None specified</td>
</tr>
<tr>
<td>American College of Physicians</td>
<td>2013</td>
<td>None</td>
<td>50-69 years</td>
<td>40-69 years</td>
<td>Annually if PSA ≥ 2.5</td>
<td>None specified</td>
</tr>
<tr>
<td>National Comprehensive Cancer Network</td>
<td>2014</td>
<td>45-49</td>
<td>50-70 years</td>
<td>Consider change in biopsy threshold</td>
<td>For 40-49 yrs: every 1-2 yrs if PSA &gt; 1 ng/ml (repeat at 50 years if PSA ≤ 1) For 50-70 yrs: every 1-2 year</td>
<td>3 ng/ml &lt; 3 ng/ml in high risk (family history/race)</td>
</tr>
</tbody>
</table>

*Kim EH et al, BMC Medicine 2015;61:1-4*
A Reasonable Plan

- Finding potentially lethal prostate cancers in men is important
- Some form of screening is necessary
- It probably would have been better to use a risk stratification model to screen younger men and also those at high risk
Limitations of Screening

- PSA and DRE: not reliable to predict disease stability/progression
- TRUS biopsy: potential risks / complications
- Frequent follow ups
- Cost
- Patient anxiety
- Subsequent treatments: more complicated
- Chance of missed opportunity for cure: disease progression, metastases, death
New Prostate Cancer Biomarkers

- New biomarkers may help avoid the false positives of PSA or avoid over treatment

- New biomarkers can risk stratify those diagnosed with cap and identify those most appropriate for AS

- Increase the benefits of screening and treatment

"Urology department. Can you hold?"
Early detection of aggressive prostate cancer
Strategy

• Simple means to identify patients at greatest risk for prostate cancer that will lead to adverse outcomes

• Need reflex blood biomarker to:
  
  • Identify patients who harbor high grade prostate cancer and would benefit from treatment

  • Avoid prostate biopsies in men with indolent (Gleason ≤ 6) or no cancers to avoid over treatment

## Where are Prostate Cancer Biomarker Test Clinically Applicable?

<table>
<thead>
<tr>
<th>Test</th>
<th>Specimen</th>
<th>Indication</th>
<th>Utility</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>phi test</strong></td>
<td>Blood</td>
<td>PSA between 2 and 10 ng/mL</td>
<td>Gives the percent likelihood of finding PC with biopsy</td>
<td>Measures 3 forms of PSA: tPSA, fPSA and pro2PSA</td>
</tr>
<tr>
<td><strong>4Kscore Test</strong></td>
<td>Blood</td>
<td>Elevated PSA</td>
<td>Predicts likelihood of a high-grade tumor (Gleason &gt; 7) upon biopsy</td>
<td>Total PSA, Free PSA, Intact PSA, and hK2</td>
</tr>
<tr>
<td><strong>ConfirmMDx</strong></td>
<td>Negative Biopsy</td>
<td>Previous negative or HGfN biopsy in last 24 months</td>
<td>Confirms a negative biopsy OR details suspicious areas on prostate map for re-biopsy</td>
<td>Levels of GSTP1, APC and RASSF1</td>
</tr>
<tr>
<td><strong>PCA3 test</strong></td>
<td>Post-DRE Urine</td>
<td>Previous negative biopsy</td>
<td>Indicates likelihood of a positive repeat biopsy</td>
<td>PCA3 and PSA RNA molecules</td>
</tr>
<tr>
<td><strong>oncotype DX</strong></td>
<td>Positive Biopsy</td>
<td>NCCN very low, low, and intermediate risk PC</td>
<td>Predicts freedom from dominant 4 or high GS and/or non organ-confined disease</td>
<td>17 genes across 4 pathways associated with tumor progression</td>
</tr>
<tr>
<td><strong>Prolaris</strong></td>
<td>Positive Biopsy</td>
<td>Active Surveillance candidates</td>
<td>Gives a 10 year mortality risk, and reclassifies as greater than, less than or equal to AUA risk group</td>
<td>46 gene expression signature of cell cycle progression genes</td>
</tr>
<tr>
<td><strong>Decipher</strong></td>
<td>Post-RP tumor</td>
<td>NCCN high-risk patients (T3 disease, positive margins, BCR)</td>
<td>Predicts likelihood of PC metastasis 5 years post-RP and 3 years post BCR</td>
<td>22 RNA biomarkers across the genome</td>
</tr>
</tbody>
</table>
INITIAL PROSTATE CANCER DIAGNOSIS
- DRE
- PSA
- Gleason primary and secondary grade

INITIAL CLINICAL ASSESSMENT
- Life expectancy ≤ 5 y and asymptomatic
  - No further workup or treatment until symptomatic, except in high- or very-high-risk groups
  - Bone scan if any of these:
    - T1 and PSA > 20
    - T2 and PSA > 10
    - Gleason score ≥ 8
    - T3, T4
    - Symptomatic
    - Pelvic CT or MRI if any of these:
      - T3, T4
      - T1-T2 and nomogram indicated probability of lymph node involvement > 10%

STAGING WORKUP
- Life expectancy > 5 y or asymptomatic
  - All others: no additional imaging

RISK GROUP
Clinically Localized:
- Very low
  - T1c
  - Gleason score ≤ 6
  - PSA < 10 ng/mL
  - Fewer than 3 prostate biopsy cores positive, ≤ 50% cancer in each core
  - PSA density < 0.15 ng/mL/g

- Low
  - T1-T2a
  - Gleason score ≤ 6
  - PSA < 10 ng/mL

- Intermediate
  - T2b-T2c or
  - Gleason score 7 or
  - PSA 10-20 ng/mL

Preferred treatment for any therapy is approved clinical trial.

bMen with clinically localized disease could consider use of a tumor-based molecular assay to stratify better risk of adverse pathology at radical prostatectomy or chance of biochemical recurrence or disease-specific mortality after radical prostatectomy.
**4K Score**

4Kscore™ Test is a reflex test to identify risk of aggressive prostate cancer

**Components**

- 4 kallikrein levels
- Total PSA
- Free PSA
- Intact PSA*
- hK2*

+ Age, DRE, and history of prior negative biopsy

**OPKO ALGORITHM**

**Results**

% risk of having aggressive prostate cancer for an individual patient

*Intact PSA and hK2 are associated with poorly differentiated prostate cancer

The PHI test measures total PSA (tPSA) in addition to two special forms of the protein: free PSA (fPSA), and pro2PSA.

- **tPSA** includes all types of PSA circulating in the bloodstream, whether free or bound to other proteins.
- **fPSA** is PSA that circulates as a free protein, unattached to any other proteins. A low percentage of free PSA (fPSA/tPSA X 100%, or %fPSA) is associated with increased prostate cancer risk.\(^6\)
- **pro2PSA** is a form of PSA that is highly expressed in prostate cancer tissue and is associated with more aggressive disease.\(^7\)

These three values are used to calculate the PHI score, which is a more accurate way to assess prostate cancer risk.

http://www.myinnovativelab.com/prostate-cancer/
• PSA screening detects cancers earlier
• Treating PSA-detected cancers may be more effective
• PSA may contribute to the declining death rate

Potential Benefits

Potential Harms

• False positives are common
• Overdiagnosis and overtreatment is a problem, but magnitude is uncertain
• Treatment-related side effects

Must Involve the patient – “shared decision-making”
Thank You

Urologists

We have been blessed with golden opportunities, we know how to go with the flow, and we make the lives of our patients a wee bit better.